FEVER FOUNDATION

FEVER

A CONCEPT ANALYSIS

A HANDBOOK FOR PHYSICIAN

Compilation of articles from

FeFCon 2020 VIRTUAL CONFERENCE

MICRO KNOWLEDGE ACADEMY

FEVER FOUNDATION

FEVER

A CONCEPT ANALYSIS

MICRO KNOWLEDGE ACADEMY

This book has been made possible by a grant from MICRO LABS LIMITED, as a service to the medical profession.

Published by:

MICRO LABS LIMITED

31, Race Course Road, Bengaluru - 560001

For free distribution to doctors under the aegis of Micro Knowledge Academy.

Disclaimer:

The editors have checked the information provided in this publication to the best of their knowledge. However in view of possibility of human errors and changes in medical science, neither the authors nor the publisher or any other person/s who has/have been involved in the preparations of this work warrants that the information contained herein is in every respect accurate or complete and therefore disclaim all the responsibility for any errors or omissions or for the results that may be obtained from use of the information contained in this publication.

FOREWORD

Fever is a characteristic feature of most infections, also found in a number of noninfectious diseases such as autoimmune and autoinflammatory diseases.

Fever is one of the most common symptoms of illness in adults , and the approach to its diagnosis and management is constantly evolving.

Understanding febrile response is vital in the diagnosis, treatment and follow-up of various diseases.

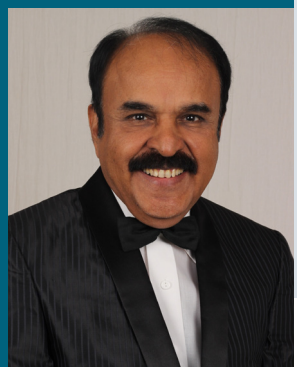
Due to the pandemic FeFCon was conducted using the digital platforms. The FeFCon 2020 virtual conference is the Third Annual National Conference of Fever Foundation which addressed various aspects of Fever.

This book is a collection of important topics about fever presented at the FeFCon 2020 virtual conference held on 20th , 21st and 22nd November, 2020 that helps in gaining better understanding about fever and its management.

Dr. Maiya M

MBBS (Mys), FRCP (lond), FRCP (Edin), FRCP (Glasg), FICP (Ind), FICC (Ind)
Chief Patron, Fever Foundation of India, Bangalore
Former Professor of Medicine, Karnataka Medical Service
Senior Physician, Rangadore Memorial Hospital, Bangalore

FOREWORD



Fever often occurs in response to infection, inflammation and trauma.

It is the balance in the interactions between pyrogens and cyrogens that determine the height and duration of the febrile response to any immune challenge.

Complexity of the febrile response may be attributable to its multi-systemic effects orchestrated by endocrine, neurological, immunological and behavioural mechanisms.

Elderly patients, as well as those who have autonomic neuropathy, immunosuppression, sepsis or are receiving continuous renal replacement therapy, may have decreased ability to produce a fever.

Early diagnosis and initiation of treatment is required for improved outcomes in patients with fever.

The FeFCon 2020 virtual , the third annual conference of the Fever Foundation addressed various aspects of Fever. This Fever Foundation Book from the FeFCon 2020 can give an insight in the management of fever in day to day clinical practice.

Dr. A. Muruganathan
Chairman – Fever Foundation CME Committee
Governor – American College of Physicians
Past Dean – Indian College of Physicians of India
Past President – Association of Physicians of India
Past President – Hypertension Society of India

PREFACE

Fever is an integral part of the inflammatory response and has therefore likely to have a physiological role in fighting infections.

Fever is recognised an ancient adaptive compensatory defence mechanism leading to immune activation, decrease in bacterial and viral growth rate, and improve host survival in response to invasion by foreign antigens.

The vast majority of fevers are associated with self-limited infections, most commonly of a viral origin, where the cause of the fever is easily identified.

Clinical interpretation of fever is often remarkably individual and highly variable.

Current practice considers the use of antipyretics a necessity in the treatment of fever.

This Fever Foundation book provides extensive information about interesting topics of fever and its management presented at The Third Annual National Conference of Fever Foundation, FeFCon 2020 virtual conference.

Happy Reading!

Dr. T S Ravindra
HOD- Mallige Hospital, Bangalore
Organising Chairperson – FeFCon

PROLOGUE

Fever Foundation is an independent, non-commercial foundation supporting the educational/ academic activities to address the unmet needs in fever management. The foundation is committed to conceptualize, invigorate programs and develop scientific initiatives aimed at providing evidence based updates to health care professionals.

Due to the pandemic, The Third Annual National Conference of Fever Foundation,was conducted using the digital platforms. FeFCon 2020 Virtual was held on 20th, 21st & 22nd November 2020. Spectacular presentations by highly esteemed and renowned speakers were delivered in the three day academic feast.

This book is the brief capture of scientific sessions that helps in gaining better understanding about fever and its inculcation in day to day practices.

Happy Reading,

Dr. Manjula S
Organizing Secretary,
FeFCon 2020

Index

Sl. No.	Content	Page No.
1	**COVID-19: AIIMS Experiences** Dr. (Prof.) Randeep Guleria	1
2	**Fever in COVID 19: A Clinico-Epidemiological Perspective** Dr. M. K. Sudarshan	9
3	**Role of doxycycline in febrile illness** Dr. Pradeep Rangappa	14
4	**Ophthalmological clues to infectious diseases** Prof. Dr. Rohit Shetty	19
5	**Febrile thrombocytopenia** Dr. Ashutosh Biswas	26
6	**Immunocompromised individuals** Dr. Chandrashekara S	31
7	**Fever in rheumatic disorders** Dr. Ritu Aneja	35
8	**Fever in pregnancy** Dr. Latha Venkataram	40
9	**Imaging for fever evaluation** Dr. Balakrishna Shetty	45
8	**Antibiotic stewardship workshop** Dr. Bhaskar Shenoy	52
9	**Antibiotic stewardship workshop** Dr. Suresh Kumar	55
10	**Interpretation of Special Laboratory Investigations in fever** Dr. GhanShyam Pangtey*, Dr. Nikita Agarwal**, Dr. Nitesh Bassi**	59

Index

Sl. No.	Content	Page No.
11	**How to work up a viral syndrome when all tests are negative** Dr. Justin Gopaldas	64
12	**Approach to tropical fevers with renal involvement/renal syndromes** Dr. Anirban Ganguli	68
13	**The importance of nutrition in immunity** Dr. A. Muruganathan	72
14	**Pro-Con Debate: Should we start broad spectrum antibiotic on day 1 in ICU patients?** Pro: Dr. Ajith Kumar A K Con: Dr. Anupam Prakash	79

COVID-19: AIIMS Experiences

Dr. (Prof) Randeep Guleria
Director and Professor of Pulmonology,
All India Institute of Medical Sciences (AIIMS), New Delhi

"Humanity has but three greatest enemies: fever, famine and war: of these by far the greater, by far the most terrible is fever" -Sir William Osler, MD 1896

Introduction

SARS-CoV-2 virus and COVID disease were unknown before the outbreak began in Wuhan, China in December 2019.[1] The disease has emerged as the major public health burden in the world, with morbidity and mortality of global community increasing day by day.[2] The clinical profile of the disease comprises of both symptomatic and asymptomatic presentations, mild to moderate illness, severe illness (severe pneumonia), severe complicated illness (ARDS, sepsis), and atypical cardiac and neurological presentations. The All India Institute of Medical Sciences, New Delhi has been extensively involved in managing patients, framing guidelines, policies and conducting research for effective management of COVID-19.[3] The present review focuses how the AIIMS frontline workers and management has risen up to the situation to tackle the pandemic effectively.

Pathophysiology of COVID-19

COVID-19 can have diverse clinical presentations comprising of cytotoxic effects, dysregulation, endothelial damage, and cytokine release syndrome. SARS-CoV-2 enters the host cells through interaction of its spike protein with the entry receptor ACE2. Type II transmembrane protease TMPRSS2 activates the influenza virus protein for membrane fusion.[4] The proposed mechanisms for

COVID-19 infection include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNFα.[5]

Case definitions

Majority of the patients are having febrile illness and possibly associated respiratory disease. The case definitions put forth by WHO are briefed below:[6]

Suspect case

A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) AND a history of travel to or residence in a location reporting community transmission of COVID -19 disease during the 14 days prior to symptom onset.

OR

A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID -19 case in the last 14 days prior to symptom onset.

OR

A patient with severe acute respiratory illness (fever and at least one signs/symptom of respiratory disease, e.g., cough, shortness of breath; and requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A suspect case or whom testing for the COVID 19 virus is inconclusive.

OR

A suspect case for whom testing could not be performed for any reason.

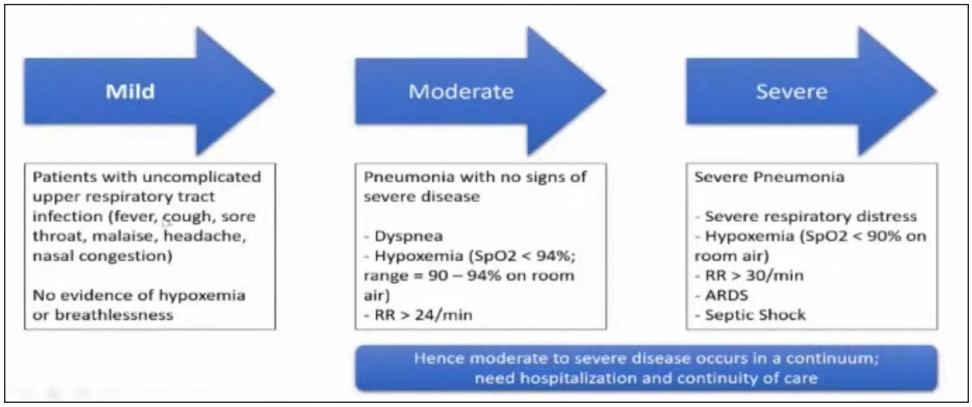
Confirmed case

A person with laboratory confirmation of COVID -19 infection, irrespective of clinical signs and symptoms.

Classification of COVID-19

Classification of COVID based on the signs and symptoms on presentation are depicted in figure 2.

Fig.2: Classification of COVID-19

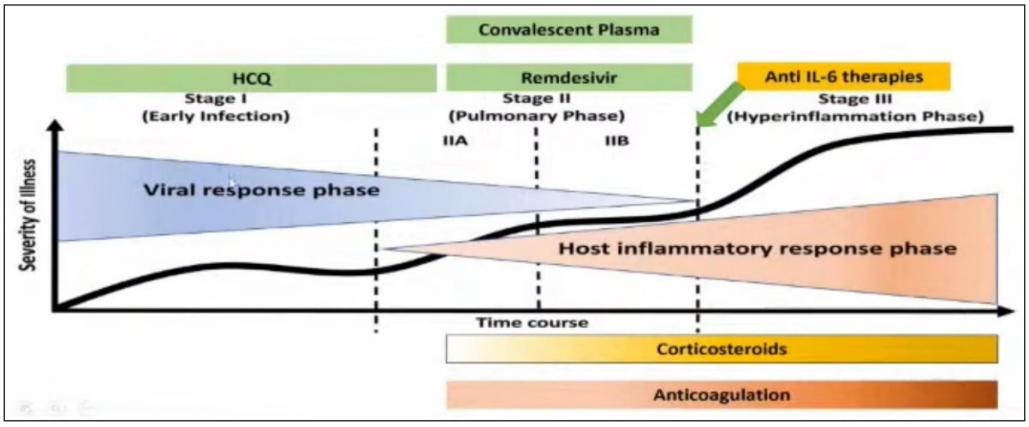


Disease course and treatment

During the early stages of the disease, majority of the subjects present with febrile illness. They may have only viremia, which tends to reduce within 7-10 days of disease onset.[7] About 15-20% of the respiratory involvement leads to hypoxemia and <5% of the cases develop cytokine release syndrome or hyperinflammation phase. In stage 2, remdesivir, steroids, anticoagulants and possibly convalescent plasma are the preferred treatment options. In stage 3, anti-IL-6 therapies can be used (Fig.3).[7]

Predominant care for hospitalized patients comprises of supportive therapy with antibiotics, antipyretics, hydration along with oxygen therapy for hypoxemic patients, antivirals (not very effective), anticoagulants, and anti-inflammatory drugs to patients with cytokine release syndrome.

Fig. 3: Disease course and treatment



Role of AIIMS in COVID management

AIIMS, Delhi is playing a paramount role in conferring effective treatment, preventing disease transmission and providing overall guidance to clinicians across the country. In March 2020, AIIMS has released guidelines on clinical management of COVID, which are intended for clinicians caring for hospitalized adults and pediatric subjects.[8] Many faculties of AIIMS are involved in guiding COVID national task force. An empowered group has been formed in collaboration with Prime Minister's office to develop COVID management strategies for the country. The author is currently chairing the clinical research group of ICMR, to oversee the COVID-related research activities.

So far, 163,082 COVID-suspected patients attended the OPD facility and nearly 9464 patients were treated till now. Evaluation of the age-wise distribution of 4000 patients admitted during the initial phase of pandemic demonstrated that most of the subjects belonged to the age group of 25-50 years. Many of these patients have associated with comorbidities, demanding the need of extra machineries and facilities.

Key challenges

The key challenges faced by the hospital faculties during the initial stages of COVID are as follows:

- Protection of healthcare workers and providing training on using protective measures and COVID-related protocols (many training programs have been conducted to improve the awareness of infection control measures)
- Motivation of healthcare workers.
- Increasing the number of intensive care beds to meet the requirement.
- Providing guidance on infrastructure and facilities of other institutions across the country.
- Creating awareness on COVID and guidance on interaction between staff and public.

Considering the pressing situation, effective response strategies have been developed by the AIIMS team to deal these challenges and the same has been briefed below:

Strategic responses

As an immediate response, on February 2020, The AIIMS has set up a COVID -19 task force constituting the following committees:

- Resource management committee
- Human resource committee
- Medical management-related committee
- Institutional Ethics Committee
- Committee for training consultants
- Diagnostic management committee

The primary objective of the task force is to ensure the proper functioning of all the departments. The task force conducted daily meeting with faculty members and nursing officers, reorganization/

prioritization of hospital services, and overseeing of emergency services. The strategic response action plan included development of infrastructure, human resource planning, process re-designing (training, procurement and stock management), testing, communication and education, research on COVID-19, academics, and donation to 'PM CARES Fund.

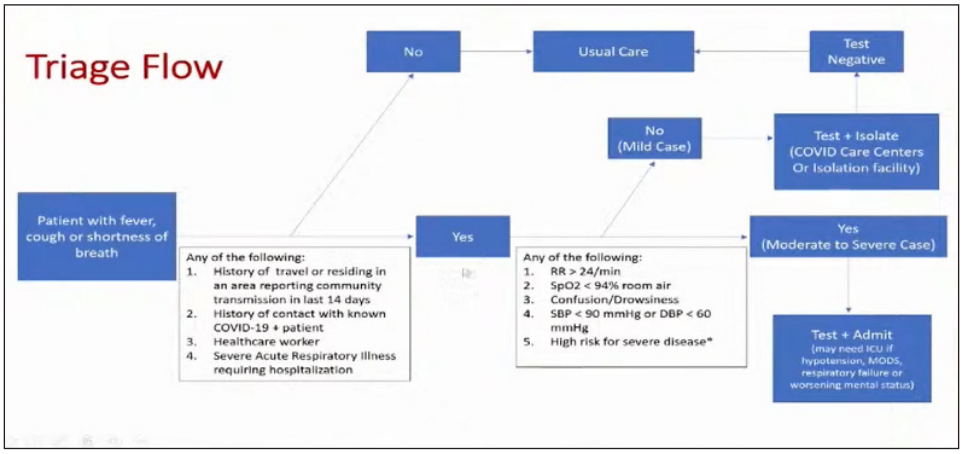
Infrastructure

The following infrastructure modifications/ reorganization were conducted as a part of COVID management response plan:

- Vishram Sadan converted to COVID care center with wards and ICU facility.
- Jai Prakash Narayan Apex Trauma Center (JPNATC) converted to COVID hospital by shifting trauma causes to main hospital.
- Main hospital equipped with fever clinic, emergency care and screening wards.
- Nearly1710 COVID beds and ICU beds were created.

During the peak, on an average 800-900 patients/day were treated at AIIMS and an effective triage flow plan was used for segregating patients (Fig. 5). Restoration of hospital services post lockdown was carried out effectively.

Fig. 5: Triage flow plan for segregating patients



The hospital has procured machinery and equipment (ventilators, high-flow nasal cannulas etc.), PPEs and other protective measures, buffer stock of key supplies, and dialysis machines exclusively for COVID patients.

Human resource planning

The planning of human resources included designation of nodal officers and teams for COVID- 19, and rostering and rotation of faculty, residents and staff. Transportation for AIIMS staff and temporary

accommodation for the doctors/ staff posted in COVID-19 specified areas were arranged.

The test facilities of the hospital have been improved by adding real-time polymerase chain reaction (RT-PCR) test, CBNAAT (cartridge based nucleic acid amplification test) and rapid antigen testing.

Validation of test kits were also provided.

Teleconsultation

The hospital is currently running the "COVID-19 National Teleconsultation Centre" (CoNTeC) on behalf of the Ministry of Health and Family Welfare, Government of India. The center is catering to clinicians across the country, who want to consult our faculties for the management of COVID-19 patients, as well as to the public. Teleconsultation has been provided to nearly 155400 COVID and non-COVID patients.[9]

Training

Training of staff for COVID care-related practices was carried out through webinars, online training modules and videos. E-platform used for these webinars were SARAL and ONTOP. Nearly 13,262 AIIMS employees were trained on infection control practices after onset of COVID 19 pandemic, and 2212 AIIMS doctors, interns, nursing officers and OTAs registered for COVID 19 special training course through the SET facility on the SARAL platform. [10,11].

The national and international training courses carried out across the country are briefed below:[3]

National training

- Clinical excellence program in each state
- National e-ICU twice a week and covered 300 hospitals
- Capacity building for COVID-19 testing in 50 mentoring institutions across the country. More than 2000 labs were equipped for COVID 19 testing.
- National Clinical Grand round on every Wednesday

International training

1. Video conference series on COVID 19 for SAARC countries
2. Management of COVID 19
3. Infection control measures in hospitals
4. Bio- medical waste management
5. Laboratory diagnostics for SARS Co-2

AIIMS faculties have also attended video conference series on COVID-19 for SARRC countries.

Research

AIIMS has constituted a research committee exclusively for overseeing COVID-19 related research. Emergency meeting for ethics committee was conducted regularly and clearance was given for 63 research projects related to COVID-19. For facilitating the funds for COVID research extramural research grants (WHO, ICMR, CSIR) and intramural research grants (AIIMS) have been established. AIIMS is the first institute to announce funding for COVID related research projects (intramural) on fast track mode.

The institute was able to publish 190 papers in various national and international journals related to COVID 19. Out of these, 58% were inter-institutional collaborative research. Important research works done and published by AIIMS are listed below:

- Use of deep neural networks to analyze chest X-rays for diagnosis of COVID
- Machine learning-based triaging of patients based on the need for hospitalization
- Randomized controlled trial of ivermectin in COVID-19
- AIIMS-NCI preliminary data on co-infection of TB, HIV, hepatitis, dengue, aspergillus mucormycosis etc.
- Correlation between the COVID-19 and tuberculosis behaviors
- NCI-AIIMS patients with malignancies (n=4200). Prognosis and behaviour of malignant patients during COVID 19.
- Poor outcomes in patients with cirrhosis and COVID-19
- Outcome of conservative therapy in COVID-19 patients presenting with gastrointestinal bleeding

Information, Education and Communication

The AIIMS doctors are providing guidance on effective clinical management of COVID patients in the ICUs of different state hospitals through tele/video consultation. They are also continuously striving to improve the awareness of clinicians and public through various modes such as information booklets, COVID portal/videos, webinars, training – national and international, national helplines and guidelines.

Conclusion

Both the faculty members and management have been actively involved in combating the epidemic, using their respective strengths to play their roles. The united effort and response strategies may serve as a model to the global community in fighting the COVID-19 pandemic, in terms of coordination, decisiveness, solidarity and leadership.

References

1. *Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020 Feb;395(10224):565–74.*
2. *Gebru AA, Birhanu T, Wendimu E, Ayalew AF, Mulat S, Abasimel HZ, et al. Global burden of COVID-19: Situational analyis and review. Human Antibodies. 2020 Jan 1;Preprint(Preprint):1–10.*
3. *AIIMS-National Grand Rounds on COVID-19 | AIIMS Covid Information Portal [Internet]. [cited 2020 Dec 3]. Available from:* https://covid.aiims.edu/cgr/
4. *Glowacka I, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 Activates the Severe Acute Respiratory Syndrome Coronavirus Spike Protein for Membrane Fusion and Reduces Viral Control by the Humoral Immune Response. Journal of Virology. 2011 May 1;85(9):4122–34.*
5. *Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nature Medicine. 2020 Jul;26(7):1017–32.*
6. *Guidelines on Clinical management of severe acute respiratory illness.pdf [Internet]. [cited 2020 Dec 3]. Available from: http://nhmharyana.gov.in/WriteReadData/userfiles/file/CoronaVirus/Guidelines%20on%20Clinical%20management%20of%20severe%20acute%20respiratory%20illness.pdf*
7. *Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. The Journal of Heart and Lung Transplantation. 2020 May 1;39(5):405–7.*
8. *Guidelines on Clinical Management of COVID – 19 | AIIMS Covid Information Portal [Internet]. [cited 2020 Dec 3]. Available from:* https://covid.aiims.edu/guidelines-on-clinical-management-of-covid-19/
9. *CoNTeC, COVID-19 National Teleconsultation Centre +91 9115444155 | AIIMS Covid Information Portal [Internet]. [cited 2020 Dec 3]. Available from:* https://covid.aiims.edu/covid-19-national-teleconsultation-centre-91-9115444155/
10. *AIIMS Telemedicine. COVID-19 (Management), AIIMS New Delhi [Internet]. 2020 [cited 2020 Dec 3]. Available from:* https://www.youtube.com/watch?v=8bcLvmqVlNg
11. *Chandrasekaran A, Thukral A, Deorari AK. E-Learning in Newborn Health – A Paradigm Shift for Continuing Professional Development for Doctors and Nurses. Indian J Pediatr. 2014 Dec;81(12):1376–80.*

Fever in COVID 19: A Clinico-Epidemiological Perspective*

Dr. M. K. Sudarshan

Chairman, Karnataka State Covid-19 Technical Advisory Committee, Govt.of Karnataka
Retd. Dean /Principal and Professor of Community Medicine, KIMS, Member, WHO expert panel on rabies and expert consultations on rabies, Geneva Founder President and Mentor - Association for Prevention and Control of Rabies in India (APCRI) & Rabies in Asia Foundation;

***G.C.Surana oration lecture delivered on 20th November, 2020 at the 3rd National Virtual Conference of Fever Foundation organized from Bangalore.**

Introduction

Since COVID-19 is still an emerging pandemic, there are several grey areas in understanding the epidemiological and clinical aspects of COVID-19. The present review focuses on the clinico-epidemiological perspective of fever in COVID-19, which may help in better understanding of the disease for preventing its community transmission and instituting effective clinical management.

Global and Indian scenario of COVID 19

The COVID pandemic has affected nearly all the countries, and as per WHO update of November 2020, more than 54 million individuals are afflicted globally. In addition, the death toll due to COVID has crossed more than 1.31 million. The current global scenario shows that cumulative number of cases was highest in the USA, India, Brazil, Russian Federation and France. Similarly, the 5 countries with highest cumulative number of deaths were the USA, Brazil, India, Mexico, and the UK (Fig. 1).[1]

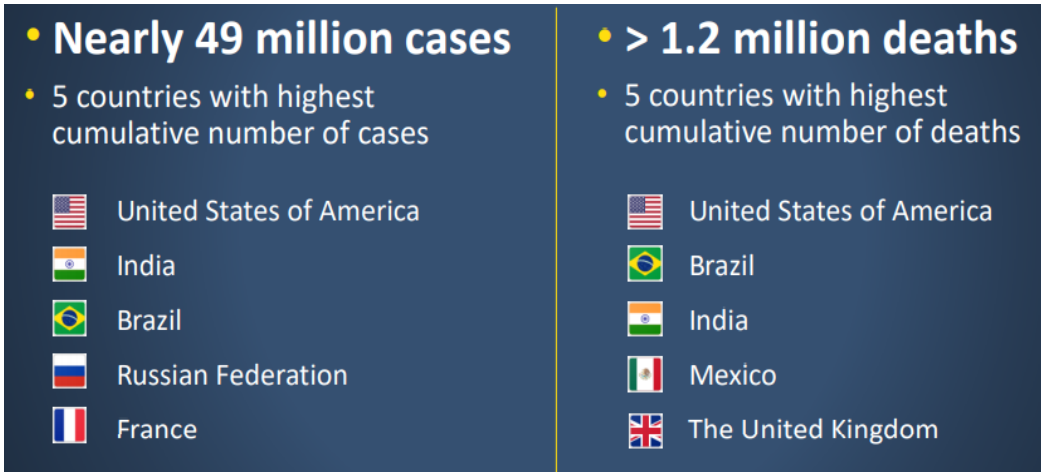


Fig.1: Countries with highest cumulative number of cases and deaths

In India, as of November 17, 2020, the total confirmed cases have crossed 88, 74, 290 with an approximate increase of nearly 30,000 cases per day. The estimate shows that the percentage of recovery from COVID -19 in the country was around 93% (N=82, 90,370) and the mortality rate was as low as 1.47% (n=1, 30,519) (Fig. 2).[2]

---

*G.C.Surana oration lecture delivered on 20th November, 2020 at the 3rd National Virtual Conference of Fever Foundation organized from Bangalore.

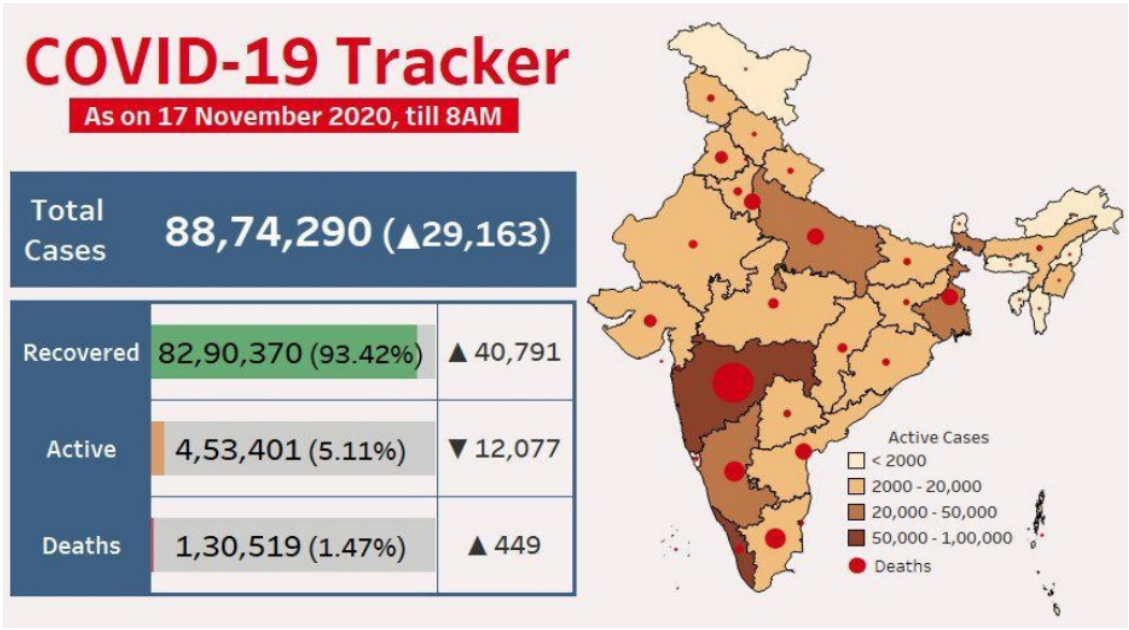
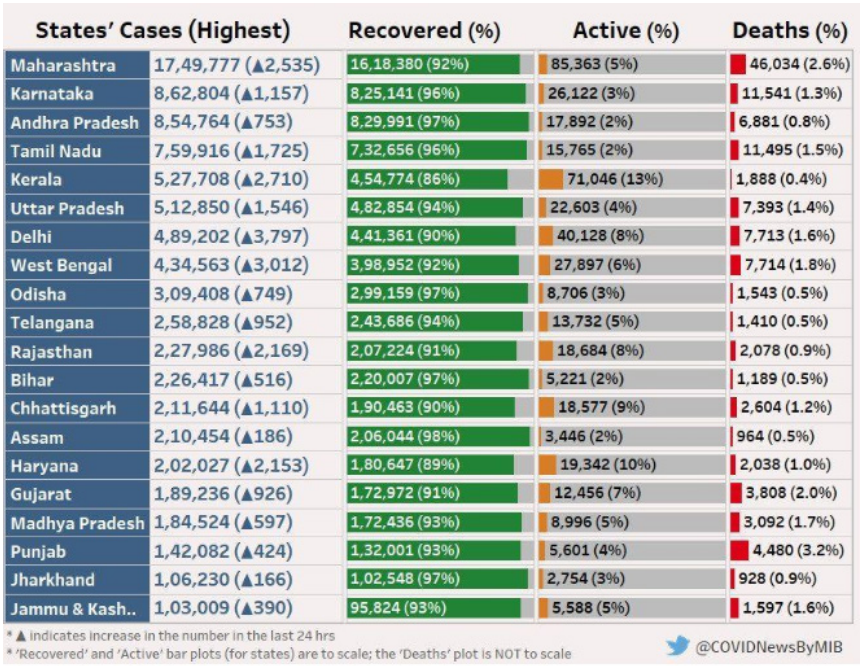


Fig. 2: India COVID scenario as on 17 November, 2020

The state-wise distribution shows that the cases were highest in Maharashtra (17, 49,777), followed by Karnataka (8, 62, 804,) Andhra Pradesh (8, 25,141) and Tamil Nadu (7, 59,916). A good surveillance is paramount for the effective management of the disease. Despite the high disease burden, the overall recovery rate was >90% in all the states (Fig. 3). The COVID-19 related mortality was more in the vulnerable groups i.e. elderly, obese, and those with comorbidities.[3]



States' Cases (Highest)		Recovered (%)	Active (%)	Deaths (%)
Maharashtra	17,49,777 (▲2,535)	16,18,380 (92%)	85,363 (5%)	46,034 (2.6%)
Karnataka	8,62,804 (▲1,157)	8,25,141 (96%)	26,122 (3%)	11,541 (1.3%)
Andhra Pradesh	8,54,764 (▲753)	8,29,991 (97%)	17,892 (2%)	6,881 (0.8%)
Tamil Nadu	7,59,916 (▲1,725)	7,32,656 (96%)	15,765 (2%)	11,495 (1.5%)
Kerala	5,27,708 (▲2,710)	4,54,774 (86%)	71,046 (13%)	1,888 (0.4%)
Uttar Pradesh	5,12,850 (▲1,546)	4,82,854 (94%)	22,603 (4%)	7,393 (1.4%)
Delhi	4,89,202 (▲3,797)	4,41,361 (90%)	40,128 (8%)	7,713 (1.6%)
West Bengal	4,34,563 (▲3,012)	3,98,952 (92%)	27,897 (6%)	7,714 (1.8%)
Odisha	3,09,408 (▲749)	2,99,159 (97%)	8,706 (3%)	1,543 (0.5%)
Telangana	2,58,828 (▲952)	2,43,686 (94%)	13,732 (5%)	1,410 (0.5%)
Rajasthan	2,27,986 (▲2,169)	2,07,224 (91%)	18,684 (8%)	2,078 (0.9%)
Bihar	2,26,417 (▲516)	2,20,007 (97%)	5,221 (2%)	1,189 (0.5%)
Chhattisgarh	2,11,644 (▲1,110)	1,90,463 (90%)	18,577 (9%)	2,604 (1.2%)
Assam	2,10,454 (▲186)	2,06,044 (98%)	3,446 (2%)	964 (0.5%)
Haryana	2,02,027 (▲2,153)	1,80,647 (89%)	19,342 (10%)	2,038 (1.0%)
Gujarat	1,89,236 (▲926)	1,72,972 (91%)	12,456 (7%)	3,808 (2.0%)
Madhya Pradesh	1,84,524 (▲597)	1,72,436 (93%)	8,996 (5%)	3,092 (1.7%)
Punjab	1,42,082 (▲424)	1,32,001 (93%)	5,601 (4%)	4,480 (3.2%)
Jharkhand	1,06,230 (▲166)	1,02,548 (97%)	2,754 (3%)	928 (0.9%)
Jammu & Kash..	1,03,009 (▲390)	95,824 (93%)	5,588 (5%)	1,597 (1.6%)

* ▲ indicates increase in the number in the last 24 hrs
* 'Recovered' and 'Active' bar plots (for states) are to scale; the 'Deaths' plot is NOT to scale

Fig. 3: State wise distribution of COVID cases

The fever component of COVID-19

Fever is a common presentation of COVID-19, common cold, flu and allergies. At the beginning of the pandemic, WHO reported gradually increasing low-grade fever (≥100.4°F or 38°C) as a common symptom affecting up to 88% of those infected. However, the present scenario shows that up to 50% of individuals with COVID-19 are asymptomatic. It has been noted that the transmissibility of the infection from asymptomatics to close contacts at house and work place were very high.[4] But after a thorough probe it was found that a vast majority of them would have had transient fever or other mild symptoms or atypical manifestations, and as a result the 'truly asymptomatics 'was only around 20-30% and the other 20-30% were 'symptomatics'. It must be noted that since beginning of the pandemic, the COVID-19 surveillance has been conducted through testing the influenza-like illness (ILI) and severe acute respiratory infection (SARI).

There is substantial literature evidence to validate that fever triggers cellular mechanism and facilitates the immune response of the body. But the intake of antipyretics like paracetemol suppresses fever or may cause adverse effects, prolong and worsen the illness.[5] In patients who had contracted

COVID-19 infection, it has been noted that majority try to suppress the fever using paracetemol and other antipyretics. This may lead to development of infection-linked morbidities, hospitalization and ultimately death.

COVID-19 cases with more severe symptoms may carry a higher viral load of SARS-CoV-2 and greater transmission capacity. A study by Kumar et al. evaluated the transmission dynamics and epidemiology of SARS-CoV-2 in patients admitted to National Institute of Mental Health and Neuro Sciences (NIMHANS), Karnataka, India. The researchers have noted that viral transmission was significantly higher from asymptomatic cases and this may have major implications on testing policies. The study also highlighted the need to prioritize the testing and treatment for symptomatic subjects[6]. On the contrary, it has been reported that isolation and treatment of symptomatic patients has led to missing asymptomatic cases, and this is more hazardous in terms of public health perspective. These observations underscore the importance of testing the suspected individuals, instead of merely managing with antipyretics.

Fever may present at the beginning of the infection or appear later during the course of the illness. It can be persistent or intermittent for a few days. Hence, Government of India has implemented a uniform discharge policy throughout the country i.e. the patients admitted to a hospital, COVID care centre or managed in home isolation/home care should be 'fever-free' for 72 hours preceding the discharge from the facility. Many of these patients after discharge, as post COVID clinical condition have developed low-grade, intermittent fever along with other symptoms such as weakness, breathlessness, cough, and loss of appetite. The post COVID clinical syndrome is now receiving wide attention and post COVID care centres are being established all over the country[7].

Screening for COVID-19

Fever clinics have been established across India to screen for COVID-19 infection.[8] However, people were initially scared to visit these clinics due to the fear of testing positive and the subsequent process of - isolation, tracing and testing of contacts & quarantining them, seal down of residence & the surrounding area . However, over a period of time many of these public health actions have changed and as a result the individuals are now visiting these centres to get tested.

The screening devices used for checking for fever among the population have certain shortcomings. Hand-held thermal scanner is the most popular fever screening device used in public places like hospitals, offices, shops & malls, cinemas, metros stations, colleges, etc. However, the chances of false readings are high, as majority of these devices are not properly calibrated before its use. Besides such faulty screening leads to missing symptomatic cases and facilitating disease transmission. The digital thermometers are given to patients, as a part of the home isolation or home-care kit. Lack of knowledge of using such thermometers, and improper cleaning of the device by many may be leading to the spread of infection.[9]

The use of thermal body screening solutions in airports and big shopping arcades assists in rapid screening of the subjects for fever. Some of them are even equipped with auto-control of the gate to prevent the exit of those having fever or in some cases even those not wearing a face mask!

Conclusion

During the current pandemic situation, patients presenting with any type of fever should be suspected as having COVID-19 and managed on the basis of specified COVID-19 policies and protocols. Aggressive search for symptomatic cases and subjecting them to screening and treatment will be key to the containment of the pandemic.

References

1. *WHO Corona virus Disease (COVID-19) Dashboard [Internet]. [Cited 2020 Nov 28]. Available from:* https://covid19.who.int
2. *Corona virus in India: Latest Map and Case Count [Internet]. [Cited 2020 Nov 28]. Available from:* https://www.covid19india.org
3. *Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health [Internet]. 2020 Aug 4 [cited 2020 Nov 28]; Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7402107/
4. *He D, Zhao S, Lin Q, Zhuang Z, Cao P, Wang MH, et al. The relative transmissibility of asymptomatic COVID-19 infections among close contacts. International Journal of Infectious Diseases. 2020 May 1; 94:145–7.*
5. *Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. Nat Rev Immunol. 2015 Jun;15(6):335–49.*
6. *Kumar N, Hameed SKS, Babu GR, Venkataswamy MM, Dinesh P, Bg PK, et al. Epidemiology of SARS-CoV-2 infection in Karnataka State, South India: Transmission dynamics of symptomatic vs. asymptomatic infections. :13.*
7. *Kaushik M, Agarwal D, Gupta AK. Cross-sectional study on the role of public awareness in preventing the spread of COVID-19 outbreak in India. Postgraduate Medical Journal [Internet]. 2020 Sep 10 [cited 2020 Nov 28]; Available from:* https://pmj.bmj.com/content/early/2020/09/10/postgradmedj-2020-138349
8. *Fever clinics to be set up as 1st point of care for Covid patients | Bhopal News - Times of India [Internet]. The Times of India. [cited 2020 Nov 28]. Available from:* https://timesofindia.indiatimes.com/city/bhopal/fever-clinics-to-be-set-up-as-1st-point-of-care-for-covid-patients/articleshow/76328296.cms
9. *Zhou Y, Ghassemi P, Chen M, McBride D, Casamento JP, Pfefer TJ, et al. Clinical evaluation of fever-screening thermography: impact of consensus guidelines and facial measurement location. JBO. 2020 Sep;25(9):097002.*

Role of doxycycline in febrile illness

Dr. Pradeep Rangappa
Senior Consultant, Critical Care Medicine, Columbia Asia Hospitals, Bangalore

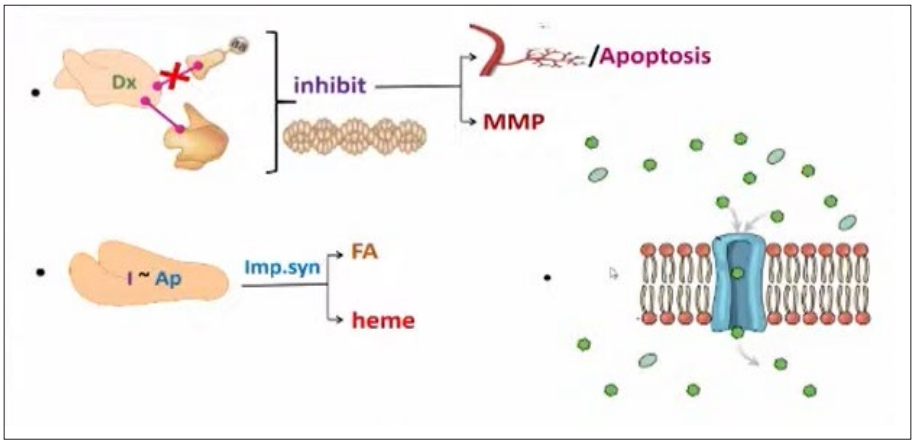
Introduction

Doxycycline was introduced in 1967 as a derivative of α-6-deoxy-tetracycline for treating malaria. It is also used as first-line antibiotic for post exposure therapy of bioterrorism agents.

Mechanism of action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. It acts by inhibiting certain matrix metalloproteases and apoptosis. It also inhibits apicoplast ribosomal subunits in *Plasmodium falciparum*, leading to impaired fatty acid synthesis and impaired heme biosynthesis. Inhibition of synthesis of heme is very important in its mechanism of action against malarial parasites. (Fig. 1).

Fig. 1: Mechanism of action of doxycycline



Pharmacokinetics and pharmacodynamics

Doxycycline is rapidly absorbed from the stomach with a half life of around 18-22 hrs. The peak concentration is reached after 2-3 hours of oral ingestion and it attains plasma concentration of about 3-5 µg/ml. For intravenous formulation, the peak concentration is 30 minutes, and it attains plasma concentration of 4-10 µg/ml. Doxycycline is fat soluble, which results in its distribution in various fluid in the body cavities such as lymphatic fluid, peritoneal fluid, colon tissue and breast milk. It enters the cerebrospinal fluid and attains a serum concentration of 14-26%. Approximately 82-90% doxycycline is bound to the protein and its highest concentration is present in bile fluid, which will be eliminated within 72 hours.

Dosage and administration

The usual dosage is 100 mg twice a day and it is available for both oral and intravenous. Maximum dose of doxycycline is 300 mg/day, whereas in children it is, 2.2 mg/kg once or twice a day and it can be used in low dose for managing skin conditions like acne and rosacea.

Clinical uses

Doxycycline is effective against Gram positive, Gram negative, other atypical bacteria and parasites. It is also effective against *Streptococcus pneumonia* and *H. Influenza*. However, *Streptococcus pneumoniae* have shown resistance of 5-25%, so doxycycline is generally administered along with β-lactam. In community-acquired pneumonia, doxycycline can be considered for ambulatory patients. It is found to be superior to cefaclor and cephalexin for managing chronic bronchitis. Doxycycline has a key advantage in managing genitourinary infections. In case of non-gonococcal urethritis, the drug is a good choice with 7 days treatment course and success rate of 97%.

Genitourinary infections

Centres for disease control and prevention guidelines advocate the use of doxycycline as a very important drug for managing pelvic inflammatory disease in combination with ceftriaxone and metronidazole.[1] However, a Brazilian study has reported that 3 doses of ceftriaxone plus azithromycin for 2 weeks had better results over ceftriaxone plus doxycycline for 2 weeks. Doxycycline is effective for managing several sexually transmitted diseases such as lymphogranuloma venereum and granuloma inguinale.[2]

Undifferentiated fever

Spotted fever or scrub typhus is caused by *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*) and the disease is spread through bites of infected chiggers. Rickettsia is sensitive to doxycycline and response is rapid for a dose of 100 mg twice a day for 5-7 days. It is also effective against Ehrlichia species and *Anaplasma phagocytophilum*. It is also used for managing Q fever at a dose of 100 mg twice a day for 14 days. Q fever can cause endocarditis, so hydroxychloroquine should be prescribed along with doxycycline for 18 months. An Indian study conducted in 1258 acute undifferentiated fever patients has reported scrub typhus as the common disease (35.9%) with mortality rate of followed by dengue, malaria, enteric fever, leptospirosis and undiagnosed fever.[3] Another Indian study also reported

scrub typhus as the commonest among the undifferentiated fever, followed by dengue, malaria, enteric fever, leptospirosis, Japanese encephalitis, and undiagnosed undifferentiated fever.[4]Another Indian study conducted in Vizag revealed scrub typhus as third commonest undifferentiated fever after malaria and dengue.[5] A study involving 44 patients reported fever as the most common symptom in undifferentiated fever and Eschar as the commonest sign reported (77%), followed by hepatomegaly in 52%. Investigations such as raised bilirubin and enzymes, and low platelets highlight the presence of scrub typhus.[6] Commonest organ dysfunction associated with scrub typhus is respiratory, followed by hematological, liver, and renal dysfuctions.[7]

Malaria

Doxycycline plays a unique role both as therapeutic and prophylactic agent. It is recommended to travellers, 2 days prior to entering an endemic area, at a dose of 100 mg once a day, followed by 4 weeks. Mefloquine, atovaquone, and proguanil are the other drugs used for treating malaria. As per the WHO guidelines, for treatment of malaria with complicated fever, doxycycline should be administered along with intravenous artesunate; and for uncomplicated fever, doxycycline should be combined with oral artesunate at a dose of 3.5 mg/kg once a day for 7 days.[8]

Leptospirosis

It is the commonest cause of undifferentiated fever, organ dysfunction and failure, and mortality in ICU. A study involving 540 patients compared parenteral cefotaxime, penicillin G sodium and doxycycline, and found out that doxycycline is superior over other drugs in reducing leptospirosis.[9] In addition, doxycycline has a prophylactic role in preventing leptospirosis; 200 mg single dose has been reported to provide a protective efficacy of 76.8%.

Miscellaneous uses

Doxycycline is recommended as a second line drug for treating *Helicobacter pylori* infection, if there is any adverse drug reaction due to first line drugs. For the treatment of Whipple's disease caused by *Tropheryma whipplei*, one-year treatment of doxycycline along with hydroxychloroquine is advocated. Doxycycline is one of the drugs used for treating infection due to *Vibrio cholerae;* however, increased recognition of resistance pattern is causing a major concern. In addition, doxycycline is used for treating brucellosis and doxycycline along with rifampicin/aminoglycosides to reduce relapse rate. Doxycycline along with minocycline is effective against nocardia, and doxycycline along with cotrimoxazole for 3 months can act as second-line drug for melioidosis caused by *Burkholderia pseudomallei*. Doxycycline 3-6 months therapy is effective against tropical sprue and for treating rat bite fever caused by *Streptobacillus moniliformis*, penicillin or doxycycline is a good therapeutic option. Moreover, 6 months doxycycline therapy is effective for treating filariasis caused by Wolbachia.

Non-infectious conditions

Non-infectious conditions that can be treated by doxycycline include autoimmune conditions such as sarcoidosis, rheumatoid arthritis and systemic sclerosis. Certain studies have suggested that doxycycline can reduce breast cancer metastasis by inhibiting matrix metalloproteases. It is effective

against potential agents of bioterrorism such as anthrax. For cutaneous anthrax, doxycycline treatment for 5-7 days is recommended, whereas for inhalational anthrax, combination therapy with doxycycline is used. Streptomycin and gentamicin along with doxycycline are very effective for managing tularemia, if it is used as a biological weapon. Plague caused by *Yersinia pestis* can be treated by doxycycline 5-7 days therapy.

Multiple antibiotic resistance

Doxycycline is effective against multiple antibiotic resistance organisms. In a study comparing doxycycline with imipenem and meropenem, doxycycline exhibited highest sensitivity of 66.67% against Acinetobacter species.[10]

Safety

Doxycycline predominantly causes skin lesions urticaria, fixed drug eruption, photosensitivity and in some cases, it may cause Stevens-Johnson syndrome and toxic epidermal necrolysis. Gastrointestinal symptoms like nausea, vomiting, diarrhoea, are common, and chronic administration can cause esophagitis and yellow discoloration of teeth. So, it recommended to take doxycycline after food with lot of water.

Resistance

Resistance to doxycycline is coded by genes *tet* and *otr.* These genes prevent the binding of doxycycline with the ribosomes. Resistance pattern is increasingly seen in Enterobacter, Pseudomonas, Legionella, Streptococcus, and Staphylococcus.

Take home points

- Doxycycline is an antibiotic with broad spectrum of activity against bacterial infection, parasites, and bioterrorism agents.
- Doxycycline is well tolerated.
- It is the drug of choice for treating rickettsial disease, brucellosis, Lyme disease, anthrax, and Q fever.
- It is effective for managing atypical respiratory diseases and sexually transmitted diseases.
- It is useful for the prevention and treatment of malaria.

References

1. *Sexually Transmitted Diseases Treatment Guidelines, 2006 [Internet]. [cited 2021 Feb 2]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5511a1.htm*
2. *Savaris RF, Teixeira LM, Torres TG, Edelweiss MIA, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol. 2007 Jul;110(1):53–60.*
3. *Abhilash KPP, Jeevan JA, Mitra S, Paul N, Murugan TP, Rangaraj A, et al. Acute Undifferentiated Febrile Illness in Patients Presenting to a Tertiary Care Hospital in South India: Clinical Spectrum and Outcome. J Glob Infect Dis. 2016 Dec;8(4):147–54.*
4. *Shelke YP, Deotale VS, Maraskolhe DL. Spectrum of infections in acute febrile illness in central India. Indian Journal of Medical Microbiology. 2017 Oct 1;35(4):480.*
5. *Boda S, Goutham VVN. Clinical Spectrum of Acute Undifferentiated Fever - An Experience from a Tertiary Care Centre. IJCMR [Internet]. 2019 Sep [cited 2021 Jan 9];6(9). Available from: https://www.ijcmr.com/uploads/7/7/4/6/77464738/ijcmr_2716_v1.pdf*
6. *Makineni VM, Boda S, Medarametla S, Palaparthi L, Ganti E. The Clinical Profile Of Scrub Typhus- A Study In A Tertiary Care Centre In Rural South India. 2(3):5.*
7. *Griffith M, Peter JV, Karthik G, Ramakrishna K, Prakash JAJ, Kalki RC, et al. Profile of organ dysfunction and predictors of mortality in severe scrub typhus infection requiring intensive care admission. Indian J Crit Care Med. 2014 Aug;18(8):497–502.*
8. *Organización Mundial de la Salud. Guidelines for the treatment of malaria. Geneva: World Health Organization; 2015.*
9. *Suputtamongkol Y, Niwattayakul K, Suttinont C, Losuwanaluk K, Limpaiboon R, Chierakul W, et al. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. Clin Infect Dis. 2004 Nov 15;39(10):1417–24.*
10. *Sandhu R, Dahiya S, Sayal P. Evaluation of multiple antibiotic resistance (MAR) index and Doxycycline susceptibility of Acinetobacter species among inpatients. Ind Jour of Microb Res. 2016;3(3):299.*

Ophthalmological clues to infectious diseases

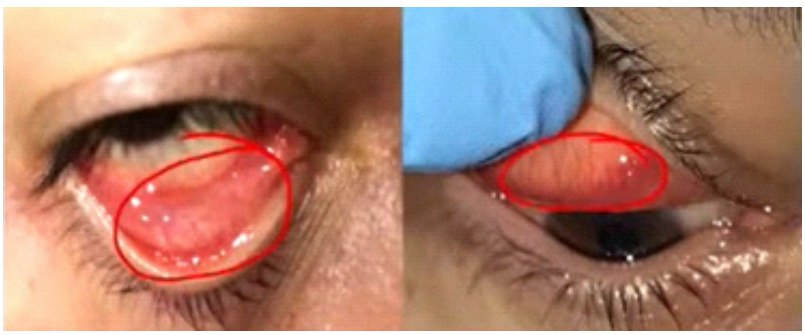
Prof. Dr. Rohit Shetty
Consultant Cornea and Refractive Surgery
Vice Chairman, Narayana Nethralaya, Bangalore

Introduction

Eyes serve as a window to infectious diseases and it is integral to examine anterior segment of cornea, uvea, inside the retina, and optic nerve to conclude the diagnosis. Dr Li Wenliang, a 34-year-old ophthalmologist who died in Wuhan Central Hospital was the whistle blower and the first person to recognize SARS-type illness, which later identified as COVID-19.[1]

One of the first signs of COVID-19 infection can be related to eye. Conjunctivitis can be related to early sign or an isolated form of COVID-19 (Fig. 1).[2] After the lung, corneal epithelial cells have been identified as the second commonest area expressing ACE2 receptors. Hence, ocular surface may serve as a possible site of virus entry and a source of contagious infection. Trehalose, a lubricating drop, is recommended for prophylaxis in individuals who are in close contact with COVID-19 patients, as it has a role in cathepsin-related pathway.[3]

Fig. 1: Follicular conjunctival reaction

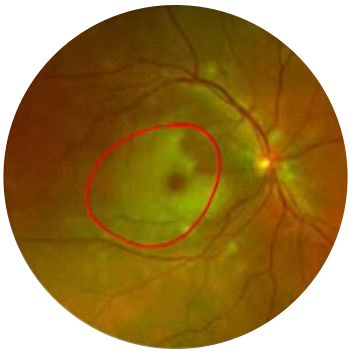


Mask-associated dry eye (MADE) is an emerging phenomenon. Long hours of wearing mask is associated with dry eye, which can be caused by air from breathing out is channelled out on top of the face mask and over the surface of the eye. The movement of the air over the eyes may cause tears to evaporate, leaving the surface of the eye dry, gritty, irritated, itchy, watery, and red.[4]

Retinal Manifestations

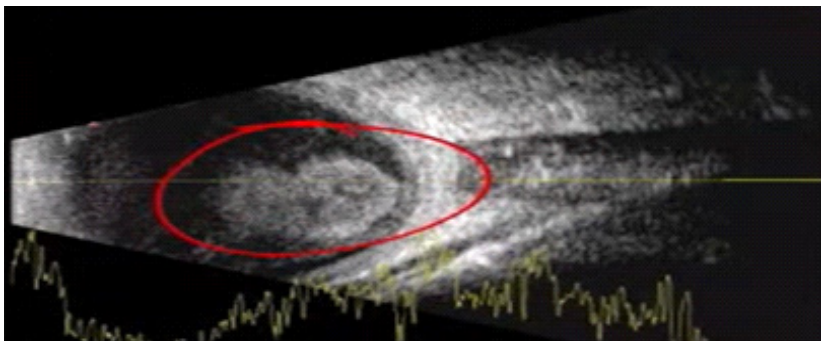
Case 1: A 66-year-old male diabetic patient was tested positive for COVID-19. After 12 days, the patient suffered from sudden loss of vision in the right eye and on diagnosis it was identified as central retinal artery occlusion (Fig. 2).[5]

Fig. 2: Central retinal artery occlusion



Case 2: A 47-year-old man who tested COVID-19 positive a month ago presented with pain and redness of eye. Extensive inflammation was noted on B-scan and on diagnosis it was identified as endogenous endophthalmitis (Fig. 3).

Fig. 3: Endogenous endophthalmitis



Infections can be due to active replicating organisms in the eye and the common infections are briefed below:

- Bacterial infections: Tuberculosis, syphilis, leprosy
- Fungal infections: Candidiasis, histoplasmosis

- Viral infections: Varicella, AIDS
- Parasitic infections: Toxoplasmosis in HIV, cysticercosis

Para infectious ocular problems are noted for epidemic retinitis (Fig. 4), rickettsia disease, dengue, chikungunya, tuberculosis, and leptospirosis (Fig. 5 and 6).[6] Hence it is paramount to conduct ocular examinations while evaluating for dengue, rickettsial disease, chikungunya, and tuberculosis.

Fig. 5: Retinitis noted in chikungunya, rickettsial disease, and dengue

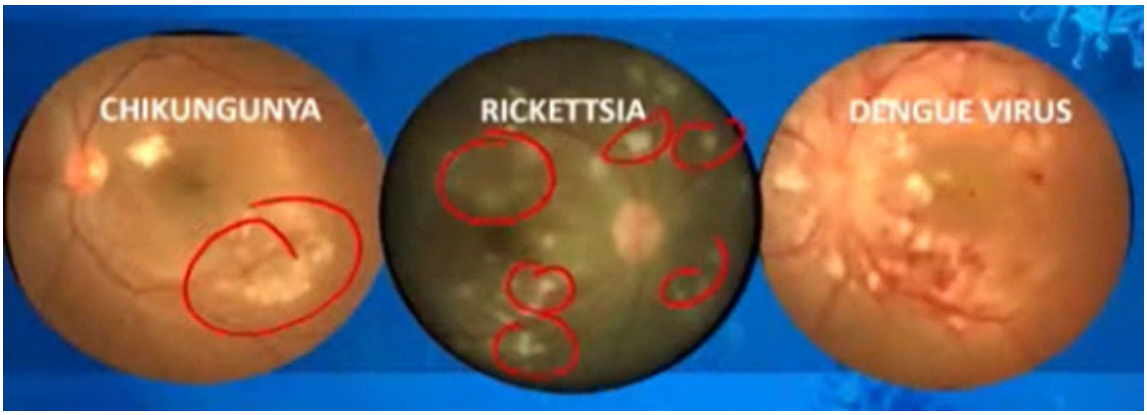
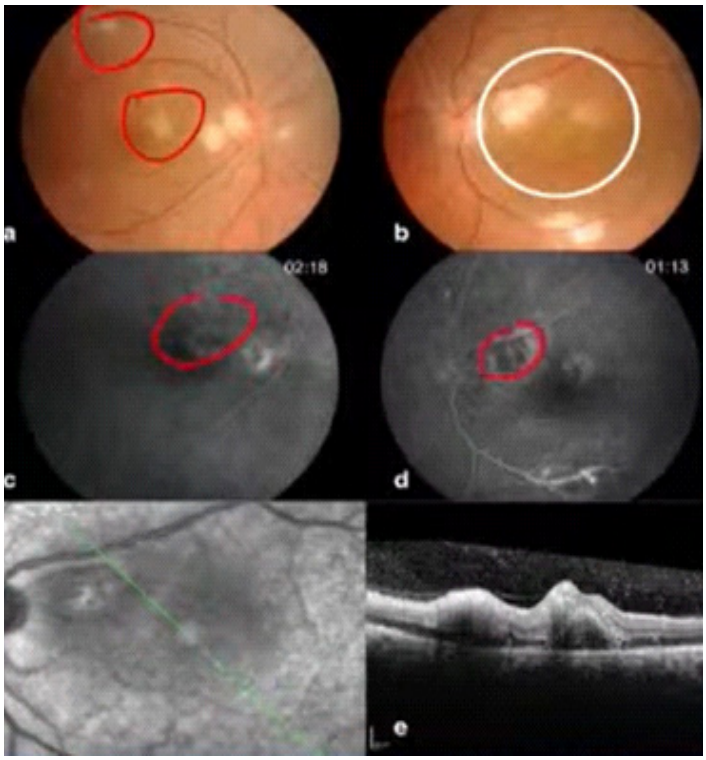
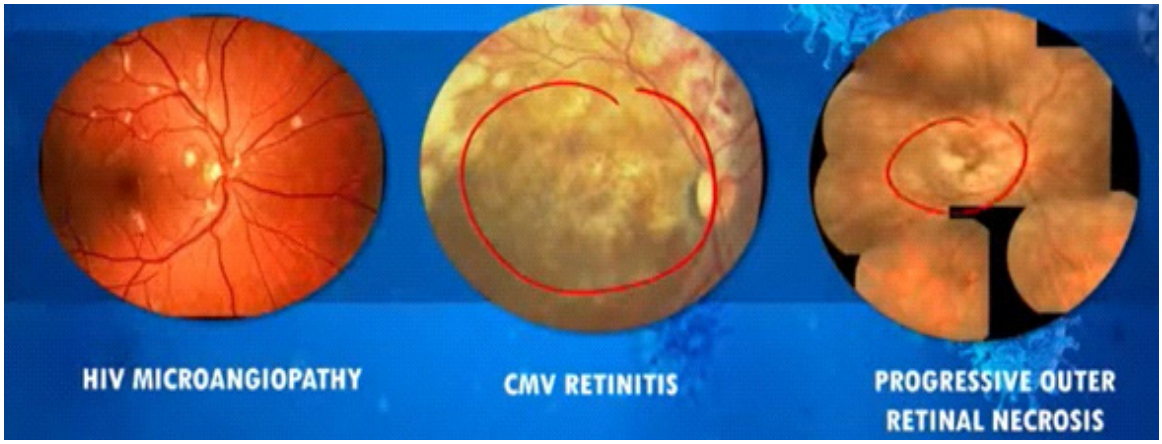


Fig. 6: Retinitis noted in rickettsial disease



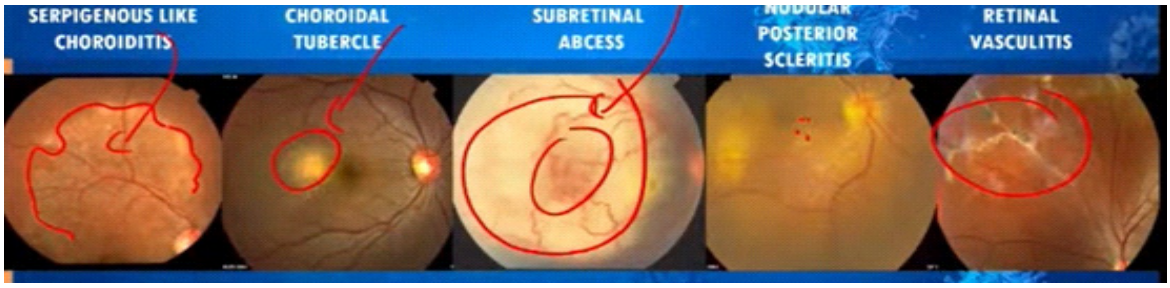
Retinal manifestations of HIV: The retinal manifestations of HIV may include CMV retinitis, progressive outer retinal necrosis, and HIV microangiography. (Fig. 7).

Fig. 7: Retinal manifestations of HIV



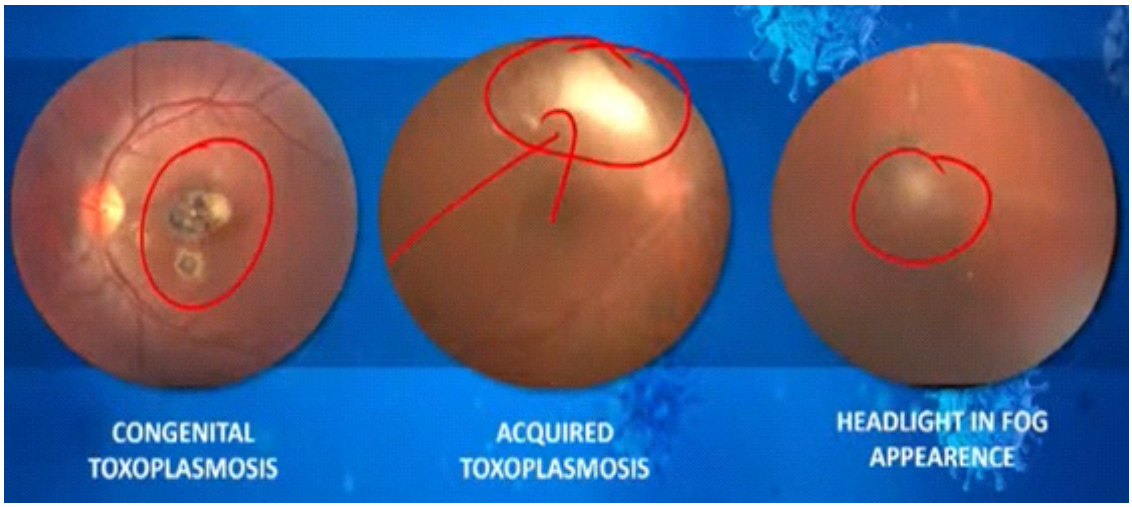
Retinal manifestations of tuberculosis: The retinal manifestations of tuberculosis may include blood retinal vasculitis, subretinal abscess, choroidal abscess in tubercle, and serpiginous choroiditis. (Fig. 8).

Fig. 8: Retinal manifestations of tuberculosis



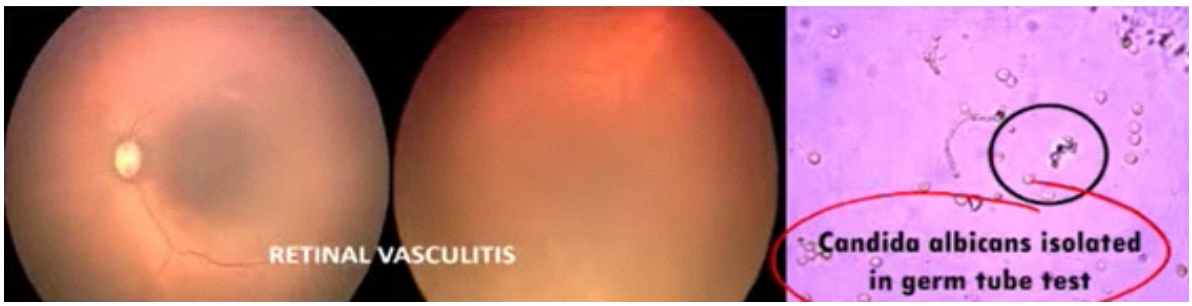
Retinal manifestations of toxoplasmosis: In retinal manifestations of toxoplasmosis, changes such as congenital toxoplasmosis, acquired toxoplasmosis and headlight in fog appearance in retina can be seen. Congenital toxoplasmosis can lead to low vision in children.

Fig. 9: Retinal manifestations of toxoplasmosis



Case 3: A premature male infant with 32 weeks of gestational age and 1200 grams weight was detected with fungal retinal vasculitis during routine screening for retinopathy of prematurity. He was identified with fungal retinal vasculitis due to *Candida albicans* and was treated with IV amphotericin B (Fig. 10).[7]

Fig. 10: Retinal vasculitis due to *Candida albicans*



Case 4: A 20-year-old presented with neck pain and headache for 8 months, and tinnitus with occasional vomiting for 3 weeks. He was identified with brisk reaction of pupil to light and optic disc edema (Fig. 11). In another case study, a large tuberculoma in the left occipital lobe was identified in MRI brain and orbit/plain and contrast view (Fig. 12).

Fig. 11: Optic disc edema

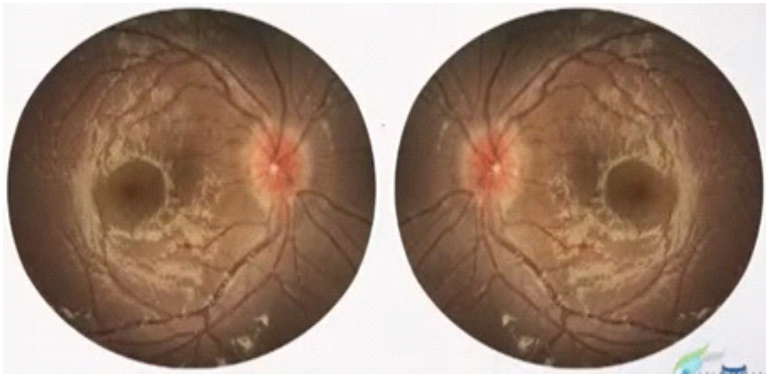
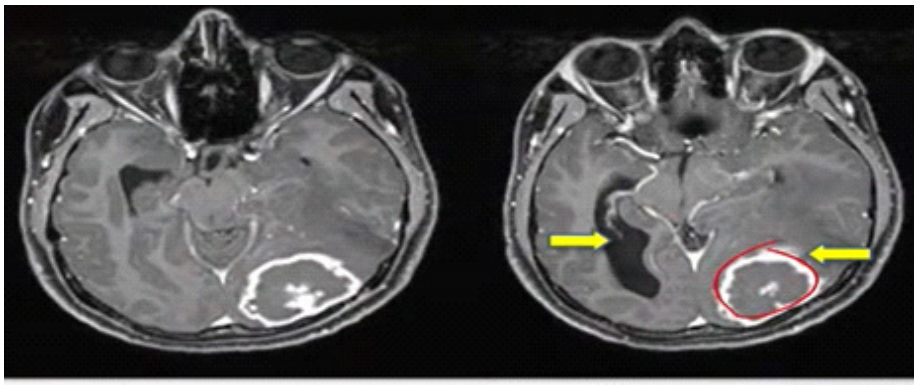


Fig. 12: MRI brain and orbit with contrast axial sections



Key points

- A prompt diagnosis is mandatory for life threatening pathologies.
- Careful ophthalmological evaluation can give clue to diagnosis and early referral.
- Multidisciplinary and multimodal imaging approach helps in early therapeutic intervention.
- Immediate referral to an ophthalmologist is important if recovered COVID-19 patients complain of eye symptoms.

References

1. *Parrish RK, Stewart MW, Powers SLD. Ophthalmologists Are More Than Eye Doctors—In Memoriam Li Wenliang. American Journal of Ophthalmology. 2020 May 1;213:A1–2.*
2. *Ozturker ZK. Conjunctivitis as sole symptom of COVID-19: A case report and review of literature. European Journal of Ophthalmology. 2020 Jul 24;1120672120946287.*
3. *Shetty R, Lalgudi VG, Khamar P, Gupta K, Sethu S, Nair A, et al. Potential ocular and systemic COVID-19 prophylaxis approaches for healthcare professionals. Indian Journal of Ophthalmology. 2020 Jul 1;68(7):1349.*
4. *COVID-19 and contact lenses: the facts you need to know – Centre for Ocular Research & Education [Internet]. [cited 2021 Jan 13]. Available from: https://core.uwaterloo.ca/covid-19/*
5. *Acharya S, Diamond M, Anwar S, Glaser A, Tyagi P. Unique case of central retinal artery occlusion secondary to COVID-19 disease. IDCases. 2020;21:e00867.*
6. *Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. J Ophthalmic Inflamm Infect. 2013 Feb 11;3:35.*
7. *Vinekar A, Avadhani K, Maralusiddappa P, Prabhu VMD, Mahendradas P, Indumathi VA. Retinal vasculitis as an early indicator of systemic candidal abscesses in a premature infant. Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}. 2011 Feb 1;15(1):96–7.*

Febrile thrombocytopenia

Dr. Ashutosh Biswas
Professor, Department of Medicine
All India Institute of Medical Sciences, New Delhi

Introduction

Febrile thrombocytopenia is the most common cause for hospital admission, which requires extensive evaluation and prompt management. It is a common problem with increased mortality and morbidity, if not diagnosed timely and treated properly. Fever can be acute febrile illness or chronic febrile illness due to infective and non-infective causes.

Severe fever with thrombocytopenia (SFTS) is an emerging infectious disease caused by Dabie banda virus (also known as the STFS virus). The major clinical symptoms include fever, vomiting, diarrhea, multiple organ failure, thrombocytopenia, leucopenia, and elevated liver enzyme levels.

Mechanisms

Fever can cause thrombocytopenia by decreased production and suppression of megakaryocyte in bone marrow, increase production of antiplatelet antibody and consumption of platelets and pseudo-thrombocytopenia. Drug-induced immunological thrombocytopenia is associated with the use of quinine, quinidine, phenacetin, methicillin, sulphonamides, gold salts and heparin. These drugs induce the production of certain antibodies and their subsequent binding to platelets and destruction. Cytostatic drugs suppress bone marrow and cause pancytopenia. B and plasma cell defects and T cell impairment can lead to both platelet and NK cell function impairment, resulting in platelet degradation and inefficient thrombopoiesis. Thromboxane A and serotonin, secreted with the activation of platelets, cause vasospasm, agglutination, and aggregation of platelets. This event subsequently contributes to endothelium damage. Both antibody-mediated and T cell-mediated responses cause platelet destruction. Imbalanced cytokine secretion stimulates the production of

pro-inflammatory cytokines such as interleukin-1, interleukin-6 and interferon-γ leading to antiplatelet antibody production. Some infections are more prone to induce platelet clearance and apoptosis or inhibition of megakaryopoiesis. Dysregulated cellular immunity leads to destruction of platelets. Antibody-mediated platelet destruction has also been enhanced by the CRP both *in vitro and in vivo*. Platelet opsonisation by autoreactive antibodies can affect platelet reactivity by modulating agonist stimulation and release of platelet secretory granules. The presence of antiplatelet antibodies increases the risk of thrombotic events, perhaps due to procoagulant microparticles released by activated platelets or associated predispositions.

Common causes

The most common causes among admitted patients were dengue infections (51.9%), rickettsial fever (27.7%), undifferentiated fever (15.6%), scrub typhus, malaria, chikungunya, enteric fever, cytomegalovirus, Epstein-Barr virus, hepatitis, mycoplasma, mycobacterium, and brucellosis.[1,2] A study by Vishnuram et al., conducted among adult patients presented with fever and thrombocytopenia, noted that out of 100 patients, 34 were dengue positive and 66 were dengue negative. The corresponding bleeding manifestations and rashes noted in dengue positive and negative patients were 29.4% and 26.4% and 12.12% and 7.57%.[3] A study by Kumar et al. involving 100 geriatric patients reported dengue (38%) as most common etiology of thrombocytopenia, followed by malaria (20%) and viral fever (15%).[4]

Clinical patterns decide the etiology in thrombocytopenia and these clinical features, as described in figure 1, can help in differential diagnosis. In a study involving 100 patients with fever and thrombocytopenia, Gondhali et al. reported that 15% patient had signs of bleeding manifestations and the remaining (85%) subjects did not have any bleeding manifestation. Among the patients with bleeding manifestations, petechiae/ purpura was the most common presentation (14%) followed by malena (4%), hematuria (2%) subconjunctival hemorrhage (1%), epistaxis (1%), hematemesis (1%) and bleeding per rectum. Out of the 15 cases who had bleeding manifestations, 3 patients had platelet count <10000/μL, 4 patients had platelet count between 11000 -20000/μL, 5 had between 21000/μL -50000 /μL, and 3 had platelet count >50000/μL. Fifty-six subjects had a definite diagnosis with dengue fever (56%), followed by septicaemia (17%), malaria (15%), HIV (5%), viral hepatitis (4%), and typhoid 3 (3%). In 15 patients diagnosed with malaria, *P. vivax* was the commonest plasmodium species noted (10), followed by *P. falciparum* (4), and mix type of *P. vivax* and P. *falciparum* infection (1). Out of the 6 mortality cases, 1 had platelet count <10000/μL, 2 had 21000- 50000/μL range and 3 cases showed >50000/μL. These findings indicate that thrombocytopenia may not be a single risk factor for mortality.[5] Comparison of diseases associated with fever with thrombocytopenia and thrombocytopenic signs reported by Nair et al., Srinivas et al. and Gondhali et al. is given in table 1 and 2.[5-7]

Fig. 1: Clinical features in thrombocytopenia

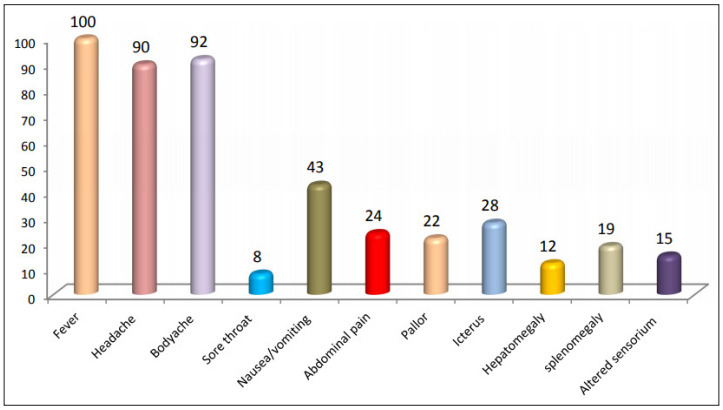


Table 1: Comparison of diseases

Disease Category	Nair et al.		Srinivas et al.		Gondhali et al.	
	No. of cases	%	No. of cases	%	No. of cases	%
Dengue fever	15	13.8	14	14	56	56
Enteric fever	16	14.7	24	24	3	3
Malaria	10	9.2	41	41	15	15
Hematological condition	17	15.6	0	0	0	0
Septicemia	29	26.6	19	19	17	17
HIV	0	0	0	0	5	5
Hepatitis B	0	0	0	0	4	4
Leptospira	0	0	2	2	0	0
Unknown	29	18.3	0	0	0	0

Table 2: Comparison of thrombocytopenic signs

Thrombocytopenic Signs (bleeding diathesis) No. of cases	Nair et al.		Srinivas et al.		Gondhali et al.	
	%	No. of cases	%	No. of cases	%	
Present	45	41.3	49	49	15	15
Absent	65	58.7	51	51	85	85

Bleeding diathesis	Nair et al.		Srinivas et al.		Gondhali et al.		
	No. of cases	%	No. of cases	%	No. of cases	%	
Petechiae / purpura	10	22.22	31	63	14	14	
SBP	31	68.00	18	37	10	10	
Others	4	9.88	00	00	00	00	

Forty-nine dengue patients had platelet counts >50,000/µL, followed by 5 patients with 21-50000/µL, and 1 each with 11-20000/µL and <10000/µL. In malaria patients, 3 had platelets in the range of > 50000/µL, followed by 7 with 21-50000/µL, 3 with 11- 20000/µL and 2 subjects with <1000/ µL. Fourteen sepsis patients had platelet count >50000/µL and 3 in the range of 21-50000/µL. Among all the cases with viral hepatitis, patients with HIV and typhoid had platelet count >50000/µL. In 45 patients with leucopenia, 39 were dengue cases, followed by 6 with malaria. However, no leucopenia was reported in patients with sepsis, viral hepatitis, HIV infection, and typhoid cases. Among the 29 patients with leucocytosis, 17 patients had septicemia cases followed by dengue (5), malaria (4), hepatitis (3), HIV (3), and typhoid (3). In 56 dengue patients, 3 patients had abnormal total bilirubin values, 17 had abnormal serum glutamic oxaloacetic transaminase levels and 13 patients had abnormal serum glutamic pyruvic transaminase levels. Out of 15 malaria patients, 11 had abnormal total bilirubin values, 7 had abnormal serum glutamic oxaloacetic transaminase levels and 3 had abnormal serum glutamic pyruvic transaminase levels. In 17 septicemia patients, all of them had abnormal levels of total bilirubin, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase. All patients of viral hepatitis showed abnormal liver function test. Out of 5 patients with HIV, 3 cases had abnormal total bilirubin values. In 3 patients with typhoid, 1 case each had abnormal total bilirubin and serum glutamic pyruvic transaminase levels. Out of 100 patients, 24 (24%) patients had abnormal renal function test. Majority of the patients with abnormal renal function test had septicemia (17), followed by dengue (3), malaria (3), and viral hepatitis (1). However, renal function test was within normal limit for typhoid and HIV patients.[5]

Diagnosis

Clinical history evaluation along with laboratory diagnosis is very important for the diagnosis of febrile thrombocytopenia. Detailed examination and laboratory test based on etiology should be carried out. Viral infections such as chickenpox, mumps, rubella, Epstein-Barr, or parvovirus can cause transient reduction in platelet counts. Factors such as bacterial, fungal, hereditary, thrombotic microangiopathies, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, immune thrombocytopenic purpura, and complete blood count should be identified for the diagnosis of febrile thrombocytopenia.

Treatment

Most treatment may depend on the etiology of fever and transfusion of platelet may not be needed in all thrombocytopenia patients. Treatment of the underlying disease may be sufficient, and immunoglobulin observation is paramount for the evaluation of thrombocytopenia <20000/cmm. In case of bleeding tendency, fresh frozen plasma treatment is used. Corticosteroids and intravenous immunoglobulin can be used as treatment. Analgesics and aspirin should be avoided, and doxycycline can be administered if the diagnosis is not confirmed.

Conclusion

Patients with fever and thrombocytopenia are commonly seen in monsoon and peri-monsoon season. It is commonly associated with vector borne diseases. Dengue is the single commonest cause (50%-

60%). Treatment of underlying cause of primary diseases leads to rapid resolution. Thrombocytopenia rarely causes fatal bleeding and >10-15% of the patients may require blood or blood products for the management of febrile thrombocytopenia. Steroid and intravenous immunoglobulin are rare options and may be useful in critical cases.

References

1. *Suneetha DK, Inbanathan J, Sahna E, Shashank MS. Common Etiology of Acute Fever with Thrombocytopenia in a Tertiary Care Hospital, Mysuru. 2016;4(1):4.*
2. *B.V R, C.S. S, Kamath V. A Study of Febrile Thrombocytopenia. IJCMR. 2019 Sep;6(9).*
3. *Vishnuram P, Natarajan K, Karuppusamy N, Karthikeyan S, Kiruthika J, Muruganathan A. Evaluation of Febrile Thrombocytopenia Cases in a South Indian Tertiary Care Hospital. J Assoc Physicians India. 2018 May;66(5):61–4.*
4. *Kumar DrS, Cn DrA, Nagaram DrD. The prevalence, etiology and patterns of thrombocytopenia among geriatric age group. Int J Clin Diagn Pathol. 2019 Jan 1;2(1):361–4.*
5. *Gondhali MP, Vethekar M, Bhangale D, Choudhary K, Chaudhary M, Kundgir A. Clinical assessment of fever with thrombocytopenia - A prospective study. :20.* **– Kindly provide proper reference**
6. *Nair PS, Jain A, Khanduri U, Kumar V. A study of fever associative with Thrombocytopenia. JAPI, Dec 2003- 51 : 1173.23.*
7. *Lohitashwa SB, Vishwanath BM, Srinivas G A.Study of Clinical and Lab Profile of Fever with Thrombocytopenia. JAPI. March 2009; 57*

Immunocompromised individuals

Dr. Chandrashekara S
Medical Director & Consultant Rheumatologist
ChanRe Rheumatology & Immunology Centre & Research, Bengaluru

Introduction

Immunocompromised individuals have a weakened immune system with impaired ability to fight infection and diseases. The primary causes for the immunocompromised state can be genetic and hereditary defects and secondary causes include protein-energy malnutrition, major elemental deficiencies, infections such as HIV, use of immunosuppressive drugs for AIDS or transplant management/ anti-malignancy drugs, and bone marrow suppression, and aplasia.[1] Careful assessment of immunocompromised individuals should focus on medications used, major drug interactions, clinical features shown, and susceptibility to microbial infections.

Immunocompromised patients are susceptible to contract various infectious agents that can cause serious diseases when compared to the general population. Such individuals may also demonstrate increased severity of disease, more rapid progression of disease and persisting chronic viral infection.[2] In certain cases, reactivation of infections like those with Epstein-Barr virus and cytomegalovirus have been noted.[3] Immunocompromised hosts need closer attention, as the clinical presentation of infection may be subtle and occult, and the signs and symptoms may be minimum and may not completely reflect the severity of the disease. Infections may be less responsive to therapy, and success of intervention depends upon the diagnosis and initiation of specific therapy. Therapy may be difficult because of drug interaction and a careful interpretation is warranted.[4]

Infection susceptibility

Infection susceptibility of an immunocompromised individual may depend on underlying condition or drugs used. Rheumatoid arthritis patients who are on methotrexate and/or on hydroxychloroquine have demonstrated increased susceptibility to infection. The impaired cellular and humoral immune functions noted in SLE are predisposing factors and high doses of methylprednisolone

or cyclophosphamide are well-known risk factors for infection susceptibility.[5] Rheumatoid arthritis patients on steroids >10 mg have demonstrated increased susceptibility to infections. The presentation of infection may be subtle and often confusing such as mild fever and cough.[6] The infective organism could be candida, *Streptococcus Viridians* and other microorganisms causing opportunistic infections.

Case study: A 32-year-old female was on regular treatment for systemic lupus erythematosus for the past 3 years. She had no pain with all healed skin rashes and her renal functions were normal. Upon consultation of a rheumatologist, she was informed to continue mycophenolate mofetil 500 mg three time daily, prednisolone 2.5 mg daily and hydroxychloroquine 250 mg daily. However, she approached a physician with complaints of mild discomfort, generalised body pain, feverish feeling, and no additional symptoms. Further examination revealed fever 100°F, pulse 120 BPM, blood pressure 120/80 mm Hg and saturation 98%. No other abnormal findings or localised signs were reported, except low-grade fever from day 1 and the patient was stable, except for increased pulse rate. The two possible management strategies are no intervention until the need of antibiotics is concluded and prescribing paracetamol as a proactive intervention.

Symptoms were subtle, and the fever may be masked by steroid use. Abscess was less painful with no localizing signs. Sepsis may be indicated by tachycardia, intermittent fever, dropping or fluctuating blood pressure, and spontaneous hypoglycemia (rare). The chances of opportunistic infections should be considered, and it is important to look for infections like oral thrush, tuberculosis, and herpes. The current patient had slightly elevated C-reactive protein, low procalcitonin level and other tests were normal. The diagnosis was concluded as viral infection, which mimicked as an SLE flare, and the symptoms improved after 2-3 days with normal C-reactive protein.

Evaluation of fever: It is important to evaluate teeth and periodontium, pharynx, chest, perineum including anus, skin, bone marrow aspiration and vascular access site, fundoscopy of eye, and tissue around nails.

Mimickers of infections: The infection may mimic pneumonitis, hepatitis and autoimmune diseases thereby making it difficult to differentiate from lupus flare. In some cases, drugs like methotrexate and cyclophosphamide may produce pneumonitis, and other drug-induced infections.[7]

Drug choice: In case of bacterial infection in immunocompromised individuals, it is advocated to use bactericidal agents. It is paramount to consider drug interactions in patients who use anticoagulants and other immunosuppressive drugs such as anti-tubercular agents, methotrexate, cytochrome P450 inhibitors.[8] Antifungal drugs can interact with other drugs used in oncology practices and those used by autoimmune and transplant patients. So, it is important to focus on the drug of choice along with immune status of the patients.

Immunosuppressants: Cessation of immunosuppressant may depend on the underlying autoimmune disease and the response of the immune system upon discontinuation of the immunosuppressants. In a patient with active lupus or associated symptoms, it is preferable to not reduce or stop the immune modulators. Whereas, in case of infections, it is preferable to hold the administration of immunosuppressant for certain period. In certain cases, it is not even possible to reverse the effect by holding the administration (e.g. cyclophosphamide). The reversal of effect of immunosuppressants

may take 2-4 weeks, and for biologics, the reversal may take 1-6 months, depending on the biologics used. Hence, withdrawing the immunosuppressant may not really change the status of patients and the decision should be taken in consultation with the respective clinician by considering various associated factors such as drug-related adverse event, disease activity and primary problem to be addressed. If the patient is on long-term steroids, it is important to consider the possibility of patients developing diabetes, altered sugar levels, hypertension, and osteoporotic fracture. In addition, it is important to consider the risk of Addison crisis, which can be precipitated by cessation of steroids. If the patient is on long-term steroids, it is advocated to maintain steroid at same doses. In patients who have contracted infection, there is an increased secretion of steroids to counter the inflammation. So, reducing the dosage of steroid can lead to infection-induced, Addison like-crisis and the demand for steroid for normal physiological functions may not be met by suppressed adrenal cortex, which could result in persistent or dropping of blood pressure.

Prevention of infection in an immunocompromised host includes complying with immunization schedules, appropriate infection control, selective screening for latent infection with appropriate treatment or suppression, and antibiotic prophylaxis.[9]

The important caveats to be considered in an immunocompromised host are as follows:

- Immunization is associated with reduced frequency of developing protective antibodies.
- Immunization is associated with lower geometric mean titre of antibody.
- It is preferrable to use inactivated vaccine rather than live virus vaccines, which can be hazardous.
- Immunization is a valuable adjunctive therapy, and it needs to be carefully utilized in patients, as it can reduce the incidence of infections and possible mortalities.

Conclusion

In an immunocompromised individual, the management is not just the sole responsibility of immunologist, rheumatologist, oncologist, or emergency care clinician. A coordinated effort of family physician and the specialist will help in effective management. It is essential for family physician to be aware of current usage of immunomodulators/suppressants and to have possible knowledge about handling of immunocompromised individual and what are the test required, which will help family physician to differentiate whether to refer the patient or not.

References

1. *Meidani M, Naeini AE, Rostami M, Sherkat R, Tayeri K. Immunocompromised patients: Review of the most common infections happened in 446 hospitalized patients. J Res Med Sci. 2014 Mar;19(Suppl 1):S71–3.*
2. *Okafor UH. Pattern of Clinical Presentations in Immunocompromised Patient. Immunodeficiency [Internet]. 2012 Oct 10.*
3. *Ivanova L, Tsaneva D, Stoykova Z, Kostadinova T. Viral Diseases in Transplant and Immunocompromised Patients. Immunopathology and Immunomodulation [Internet]. 2015 Nov 18*
4. *Pierce KK. Chapter 40 - Immunocompromised Host. In: Parsons PE, Wiener-Kronish JP, editors. Critical Care Secrets (Fifth Edition) [Internet]. Philadelphia: Mosby; 2013 [cited 2021 Mar 16]. p. 277-92. Available from: https://www.sciencedirect.com/science/article/pii/B9780323085007000412*
5. *Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus. 2013 Oct;22(12):1286–94.*
6. *Youssef J, Novosad S, Winthrop K. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am. 2016 Feb;42(1):157–76.*
7. *Jung J-Y, Suh C-H. Infection in systemic lupus erythematosus, similarities, and differences with lupus flare. Korean J Intern Med. 2017 May;32(3):429–38.*
8. *Breathnach SM, Smith CH, Chalmers RJG, Hay RJ. Systemic Therapy. In: Rook's Textbook of Dermatology [Internet]. John Wiley & Sons, Ltd; 2010 [cited 2021 Mar 16]. p. 1–53. Available from:* https://onlinelibrary.wiley.com/doi/abs/10.1002/9781444317633.ch74
9. *Risi GF, Tomascak V. Prevention of infection in the immunocompromised host. American Journal of Infection Control. 1998 Dec 1;26(6):594-606.*

Fever in rheumatic disorders

Dr. Ritu Aneja
Specialist Adult Rheumatologist, Sheikh Shakhboot Medical City (in partnership with Mayo Clinic), UAE.

Introduction

Rheumatologic assessment of febrile patients is necessary in the following scenarios: fever associated with known rheumatic diseases, fever with musculoskeletal symptoms, and fever of unknown origin with underlying rheumatologic cause. The causes of fever of unknown origin can be infection, malignancy, non-infectious inflammatory diseases (NIID), and miscellaneous causes. Nearly 30% of patients with long-term unexplained fever or fever of unknown origin are eventually diagnosed with rheumatologic diseases. NIID include autoimmune, autoinflammatory, granulomatosis and vasculitis. It may be difficult to diagnose these diseases, as they have standard set of diagnostic criteria and no gold standard test.

Etiologies of fever

A study involving 1,641 patients with fever of unknown origin by Zhou et al. reported that connective tissue diseases were responsible for 19.26% (316) of cases. Among 316 cases, adult-onset Still's disease was the most common (89), followed by SLE (31), systemic vasculitis (29), necrotizing lymphadenitis (28), Sjogren's syndrome (23), polymyalgia rheumatica (12), dermatomyositis (12), and rheumatoid arthritis (11).[1] The study by Zhai et al evaluated 215 cases with fever of unknown origin and found that connective tissue diseases were one of the common causes (69), which includes adult-onset Still's disease, vasculitis syndromes, SLE, polymyositis, rheumatoid arthritis, panniculitis, Sjogren's syndrome and undifferentiated connective tissue diseases.[2] Zenone et al. reported that non-infectious inflammatory disorders represented the most prevalent category (35.5%) compared to infectious disorders (30.20%) upon evaluating 144 cases adults with fever of unknown origin and majority of cases were suffering from giant cell arteritis and polymyalgia rheumatica.[3] In a study involving 98 patients in Saudi Arabia, Moawad et al. reported that the most frequent diagnostic

etiology was infectious (32.7%), whereas 14.3% patients had connective tissue diseases such as SLE, adult-onset Still's disease, rheumatoid arthritis and Behcet disease.[4] Kejariwal et al. reported 11% patients had collagen vascular disease upon evaluating 100 patients with pyrexia of unknown origin,. The most common disease noted was SLE followed by Takayasu's arteritis, mixed connective tissues, ankylosing spondylitis, and polyarteritis nodosa.[5] A study conducted among 152 patients with fever of unknown origin in north India reported that 19.7% patients had NIID and the most common disease was adult-onset Still's disease.[6] The literature review shows that the most frequently diagnosed rheumatologic diseases in patients with fever of unknown origin from different populations are adult-onset Still's disease, large vessel vasculitis including temporal arteritis and Takayasu arteritis, polymyalgia rheumatica, unclassified vasculitis and sarcoidosis.

Adult-onset Still's disease: It is an archetypal febrile autoimmune disease, and the most common symptoms is fever. Fever is diurnal in nature, reaching a peak > 40°C in the early evening, with normal interfebriile episodes. It is accompanied by a characteristic salmon-pink rash, and both the fever and rash subside completely within hours. Adult-onset Still's disease is a diagnosis of exclusion and it shows markedly elevated serum ferritin. However, it cannot be considered as a gold standard test, as elevated levels are found in other conditions as well. As per Yamaguchi criteria, major criteria for Adult-onset Still's disease include persisting fever >39°C, arthralgia or arthritis, typical rash and leukocytosis >10,000/mm^3 with >80% polymorphonuclear cells. Minor criteria include sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM). Exclusion criteria include infections, malignancies mainly malignant lymphoma, and other rheumatic diseases.[7] Hence it is highly challenging to diagnose adult-onset Still's disease, and differentiating from lymphoma poses a diagnostic difficult. Lymph node biopsy is required to rule out malignancy.

Systemic lupus erythematosus: Fever, usually early in the disease course, is a common manifestation of SLE and is estimated to occur in 36-86 % of the patients. The reported prevalence of fever attributed to SLE has declined progressively due to frequent use of NSAIDs. CRP levels can be a valuable diagnostic aid, and it has been reported to have a diagnostic specificity of 84%.[8]

Vasculitis: The clinical and pathological features may depend on the site and type of blood vessels involved. Giant cell arteritis and Takayasu's arteritis are the two systemic vasculitides affecting the aorta. Fever is a less common presentation in patients with granulomatosis with polyangiitis (GPA, formerly called Wegener's). Only a quarter of patients have been documented with fever as presentation. Temporal arteritis, rheumatoid arthritis, and polymyalgia rheumatica account for 25%-31% of causes in elderly. Temporal arteritis represents 17% of the cases of fever of unknown origin, especially in elderly patients. Systematic illness with malaise, anorexia, night sweats, weight loss and depression are not uncommon and seen in almost 50% of the patients. Fever can be usually low or may be the presenting clinical manifestation and may be misinterpreted as infection or malignancy.[9] The features of giant cell arteritis such as headache, tender temporal arteritis, decreased temporal artery pulse, jaw claudication, raised ESR assist in diagnosis and delay in diagnosis can cause vision loss or stroke in patients. Ultrasound of temporal arteries is recommended as the first imaging modality in patients with suspected predominantly cranial giant cell arteritis.[10] Takayasu's arteritis is

an important differential in patients with recurring fever and unexplained elevations in inflammatory markers.

Polymyalgia rheumatica: It is usually seen in elderly patients and systemic symptoms include headache, fatigue, depression, fever, weight loss, and the hallmark symptoms are pain and stiffness in neck, hip and shoulders. There is a possibility of malignancy masquerading as polymyalgia rheumatica. However, the presentation of metastatic malignancy is rare. Malignancies reported to mimic polymyalgia rheumatica include solid tumors of the kidney, stomach, colon, lungs, pancreas, uterus, and ovaries, metastatic prostate cancer, and hematologic malignancies such as multiple myeloma and lymphoma.

Sarcoidosis: It is a multisystem disorder of unknown etiology in young adults. Typical features include bilateral hilar adenopathy, and reticular opacities. Common presenting symptoms include cough, dyspnoea, chest pain, and eye/skin lesions. Biopsy of accessible peripheral lesions such as cutaneous lesion, palpable lymph nodes, and conjunctival lesions may help in diagnosis. It is important to exclude infections and malignancy.

Infectious arthritis: It can be monoarticular or polyarticular. Argen et al. reported that 37 out of 42 cases of septic arthritis were febrile.[11] A Scotland- based prospective study evaluating the clinical features of septic arthritis reported the rate of occurrence of fever as only 44%.12 The fever was less frequent in patients with co-existing rheumatoid arthritis (43% compared to 70% of patients without rheumatoid arthritis).[12] The possibility of suppression of febrile response by anti-rheumatic drugs cannot be ruled out.

Rheumatoid Arthritis: Fever is not common in rheumatoid arthritis. Patients usually present with malaise and fatigue. Rarely, patient with aggressive disease onset may present with florid polyarticular synovitis accompanied by fever. The systematic pattern of disease is seen in <5% of patients. It is important to rule out alternate diagnosis, especially malignancy.

Seronegative inflammatory arthritis: The systemic symptoms of seronegative inflammatory arthritis like psoriatic arthritis and spondylarthritis including ankylosing spondylarthritis are generally confined to fatigue and malaise. Fever is not reported in published literature and the relationship between reactive arthritis and fever has not been well described. In patient with known rheumatic disease having fever, the differential diagnoses include disease activity, infection, cancer, drugs, and vasculitis.

Fever in SLE: Serious infections are a major cause of morbidity among lupus patients and should be considered in all immunocompromised SLE patients with fever. Large majority of infections, including fungal, can be related to immunosuppressive therapy and are a common cause of death. Viral infections are also common, including parvovirus B19, Epstein-Barr virus, cytomegalovirus, varicella-zoster, and human papillomavirus. Mycobacterial infections, including non-tuberculosis, have been noted to be more frequent in patients with SLE. Fever can only be attributed to SLE, if other causes are excluded. The etiologies of fever reported in 487 SLE patients by Zhou et al. were as follows: 54.5% of patients due to infection, 42% related to SLE, 1.6% due to both SLE activity and infection, 0.8% each due to malignancy and 0.8% due to miscellaneous causes. Systemic Lupus erythematosus fever could not be suppressed by a higher dose of steroids usually had a severe lupus encephalopathy and hemophagocytic syndrome.[13] Rovin et al defined SLE with fever with the following e criteria:

absence of infection despite extensive testing, presence of an illness typical of active SLE, and accompanying fever, if there is no evidence of infection despite escalation of immunosuppression.[14] In clinical practice, distinguishing fever associated with a lupus flare from other causes of fever is challenging. It needs detailed history and examination for other features of active lupus or localized infection. Presence of leucopenia, lymphopenia, thrombocytopenia, Hemolytic anemia, low serum complements, raised double stranded DNA usually point towards active lupus and high c-reactive protein indicates likelihood of infection. Fever in the setting of moderate or high doses glucocorticoids can strongly indicate infection particularly if other signs of active lupus are absent.

Macrophage activation syndrome: Macrophage activation syndrome is seen in patients with juvenile idiopathic arthritis, adult-onset Still's disease, SLE and other rheumatologic diseases. It is an aggressive and life-threatening syndrome of excessive immune activation. The symptoms include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenia, high serum ferrtin, and liver function abnormalities. Pathognomonic feature of macrophage activation syndrome is hemophagocytosis.

Investigations

The recommended investigations in patients with rheumatologic disease and fever include complete blood count, c-reactive protein, ESR, coagulation studies, serum ferritin, liver function tests, triglycerides, urine sediment and protein, blood cultures, urine, sputum, synovial fluid, cerebrospinal fluid, gram stain, fungal smears, antinuclear antibody, anti- double stranded DNA, serum complements, antineutrophil cytoplasmic antibodies, rheumatoid factor, procalcitonin, hepatitis serology, viral serology, X-rays, echo, ultrasound, computed tomography, MRI, bone marrow aspirate biopsy, tissue biopsy, skin examination and fluorodeoxyglucose -positron emission tomography. A fundamental disadvantage of the 18F-FDG PET/CT scan is that it can locate source of pyrogens, but unable to distinguish between malignant, infectious, or inflammatory processes, although it is useful in large vessel vasculitis, extra cranial giant arteritis, and Takayasu's arteritis.

Key points

- Low-grade fever is common in chronic inflammatory diseases.
- Patients with rheumatic disease on immunosuppressive drug are predisposed to serious opportunistic infections.
- It is important to exclude infection and malignancy.
- Use of high steroids in the presence of infection can result in fatal sepsis.
- High index of suspicion is warranted in elderly patients with non-constitutional disease.

References:

1. *Zhou G, Zhou Y, Zhong C, Ye H, Liu Z, Liu Y, et al. Retrospective analysis of 1,641 cases of classic fever of unknown origin. Annals of Translational Medicine. 2020 Jun;8(11):690–690.*
2. *Zhai Y-Z, Chen X, Liu X, Zhang Z-Q, Xiao H-J, Liu G. Clinical analysis of 215 consecutive cases with fever of unknown origin: A cohort study. Medicine (Baltimore). 2018 Jun;97(24):e10986.*
3. *Zenone T. Fever of unknown origin in adults: Evaluation of 144 cases in a non-university hospital. Scandinavian Journal of Infectious Diseases. 2006 Jan 1;38(8):632–8.*
4. *Moawad MA, Bassil H, Elsherif M, Ibrahim A, Elnaggar M, Edathodu J, et al. Fever of unknown origin: 98 cases from Saudi Arabia. Ann Saudi Med. 2010;30(4):289–94.*
5. *Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. Journal of Postgraduate Medicine. 2001 Apr 1;47(2):104.*
6. *Pannu AK, Golla R, Kumari S, Suri V, Gupta P, Kumar R. Aetiology of pyrexia of unknown origin in north India. Trop Doct. 2021 Jan;51(1):34–40.*
7. *Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992 Mar;19(3):424–30.*
8. *Timlin H, Syed A, Haque U, Adler B, Law G, Machireddy K, Manno R. Fevers in Adult Lupus Patients. Cureus. 2018 Jan 22;10(1):e2098. doi: 10.7759/cureus.2098. Erratum in: Cureus. 2018 May 1;10 (5):c12.8*
9. *Turkulov V, Brkić S, Sević S, Marić D, Tomić S. Fever of unknown origin in elderly patients. Srp Arh Celok Lek. 2011 Feb;139(1–2):64–8. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Annals of the Rheumatic Diseases. 2018 May 1;77(5):636–43.*
10. *Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Annals of the Rheumatic Diseases. 2018 May 1;77(5):636-43.*
11. *Long B, Koyfman A, Gottlieb M. Evaluation and Management of Septic Arthritis and its Mimics in the Emergency Department. West J Emerg Med. 2019 Mar;20(2):331–41.*
12. *Gupta MN, Sturrock RD, Field M. A prospective 2 year study of 75 patients with adult onset septic arthritis. Rheumatology. 2001 Jan 1;40(1):24–30.*
13. *Zhou WJ, Yang C-D. The causes and clinical significance of fever in systemic lupus erythematosus: a retrospective study of 487 hospitalised patients. Lupus. 2009 Aug;18(9):807–12.*
14. *Rovin BH, Tang Y, Sun J, Nagaraja HN, Hackshaw KV, Gray L, et al. Clinical significance of fever in the systemic lupus erythematosus patient receiving steroid therapy. Kidney Int. 2005 Aug;68(2):747–59.*

Fever in pregnancy

Dr. Latha Venkataram
Lead Consultant, South Bangalore OBG Doctors and Associates
Rangadore Hospital, Unit of Shringeri Sharada Peetham Trust, Bangalore

Introduction

Fever during pregnancy >38^{0}C requires careful assessment and monitoring and one recorded temperature of >38^{0}C is not sufficient to diagnose pyrexia. Fever is identified as one of the oldest clinical indicators of the disease, irrespective of infective or non-infective etiology. It is important for obstetricians to exclude pregnancy related-causes of fever, as the prevalence of temperature ≥38^{0}C following spontaneous vaginal delivery in women is estimated to be 6-9%. The incidence of microbial and viral infections in women following pregnancy are estimated to be nearly 1/3 and 5% respectively. Pyrexia of unknown origin can be due to autoimmune disorders, tuberculosis, and malignancy.

Pregnant women can be exposed to any of the common infections during pregnancy, labour, and puerperium. Women during labour and puerperium are more susceptible to genitourinary infections and women who had undergone C-section have a 5-20-fold greater risk for severe infections. It is also important to consider effect of medications on the infant and the fetus. Some infections are more serious in pregnant than non-pregnant because of the risk for vertical transmission to the fetus or infant. [1]

Determinants

The developing active immune system of the fetus can modify the maternal response to infection. The evolution of immune system during pregnancy, as the foetus matures, and diverse response to infection depend not only on the infecting organism but also on the pregnancy stages. It is important to consider the stage of fever occurrence, whether it is peri- or post-natal period. Normal temperature does not exclude sepsis, as paracetamol and other analgesics may mask pyrexia.

Anatomic and physiological changes

Respiratory system: Women are prone to lower respiratory tract infection due to relaxation of lower esophageal sphincter and changes in diaphragmatic course and pulmonary volume. Decrease in oxygen supply and modification of pulmonary volume associated with increase in capillaro-alveolar permeability and decrease in oncotic pressure can lead to respiratory failure, early pulmonary edema and acute respiratory distress syndrome. [2]

Genitourinary tract: Urinary infections account for 10% of primary consultations during pregnancy. In addition, the chances of pyelonephritis are higher due to compression of ureters by the gravid uterus and enhanced vesicoureteral reflux during pregnancy.

Immune changes: Pregnancy is a modified immune state. Adaptive immunity depends on T and B cell and it is highly specific. However, it is reduced during pregnancy, particularly the T-cell functions, which can make the women more prone towards viral infections.

Effects of fever: Fever in pregnancy can cause miscarriage, congenital abnormalities, prematurity, still birth and growth restriction. Fever in embryonic period of pregnancy can be associated with neural tube defects, oral clefts, and congenital heart anomalies. Antipyretics are beneficial in reducing adverse pregnancy outcomes in women experiencing fever. Exposure to hyperthermia and inflammation during labour affects neurological development such as neonatal encephalopathy, cerebral palsy and seizures and this can lead to long-term neurodevelopment problems such as autism and attention-deficit/hyperactivity disorder. The use of antipyretics in febrile pregnant women is imperative to help prevent intrauterine hyperthermia and possible fetal damage.[3]

Sepsis: Untreated fever during pregnancy increases the risk of sepsis, which can be insidious with rapid deterioration due to hypervolemia. A state of hypervolemia can be due to increase in cardiac output, stroke volume, left ventricular compliance, blood and plasmatic volume, decrease in systematic vascular resistance, and stability in myocardial contractility. Septic shock can be masked and there can be an increase in coagulation factors, and this can potentially exacerbate disseminated intravascular coagulation. Hence, there are chances of missing sepsis and identifying it only in advanced stages and respiratory alkalosis narrows the capacity to compensate metabolic acidosis during sepsis. Sepsis can develop very quickly, which needs urgent attention and strong suspicion. Use of a modified early obstetric warning score may assist in recognising critically unwell patients. Women with suspicion of severe sepsis need early diagnosis, administration of intravenous broad-spectrum antibiotics within golden hour and review by senior doctors to improve outcome and avoid significant maternal and neonatal morbidity and mortality (Fig. 1).[4,5] Mortality is higher for sepsis and appropriate investigations and management can reduce adverse outcomes, unnecessary interventions, and anxiety.

Fever in pregnancy: it is important to differentiate fever related to pregnancy from viral or bacterial infections. In addition, it is important to understand the maternal and fetal risks, and safety of the treatment during pregnancy and breast feeding. Pregnancy-related fever is mainly related to chorioamnionitis, breast abscess, endometritis, septic abortion, perineal infection, cerebral venous thrombosis, deep vein thrombosis, scars infection, puerperal ovarian vein and necrotizing fascitis. Obstetric procedures that can be risk factors for sepsis or fever are amniocentesis and invasive

procedures. Cervix suture, prolonged rupture of membrane, prolonged labour, >5 vaginal examinations, vaginal trauma, Caesarean section, and retained placental fragments are probable reasons for elevated body temperature. The risk factors related to the women can be obesity, diabetes, impaired glucose levels, immunosuppression, anemia, sickle cell disease, high vaginal discharge, low socioeconomic status, and history of pelvic and streptococcus B infections. Associated symptoms such as rash should be examined carefully when assessing women with dark skin, and the appearance of rash may not be the same as that seen in those with lighter skin.

Clinical syndromes associated with viral infection in pregnancy: Undifferentiated fever is associated with cytomegalovirus, rubella, enteroviruses, Epstein-Barr virus, measles, parvovirus B19, and West Nile virus. Fever and non-vesicular rash can be related to rubella, measles, echoviruses, Epstein-Barr virus, parvo B19, and cytomegalovirus. Fever and arthritis are associated with rubella, parvovirus B19, and enteroviruses. Fever and neurologic signs are associated with herpes simplex virus, West Nile virus, and polio. Vesicular rash and genital ulcer are associated with varicella zoster virus and herpes simplex virus.

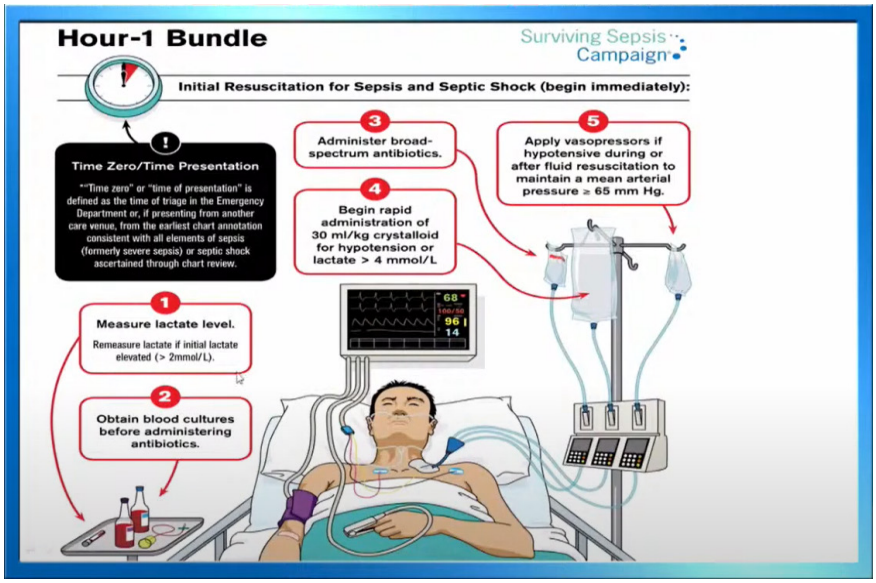
Clinical red flags: Red signs and symptoms in pregnancy are pyrexia >38^{0}C, sustained tachycardia > 90 beats/per minute, breathlessness, abdominal or chest pain, diarrhea or vomiting, uterine or renal angle pain and tenderness, when woman is generally unwell or seems unduly distressed. Red signs and symptoms should prompt urgent referral for hospital assessment.

qSOFA score: qSOFA score predicts mortality rate and identify patients with suspected infection and who are at high risk for poor outcome.[6] The differences between qSOFA criteria and score and obstetrically modified qSOFA score are briefed in table 1.

Table 1: Differences between qSOFA criteria and score and obstetrically modified qSOFA score

	qSOFA criteria and score		Obstetrically modified qSOFA score	
Parameters	Score 0	Score 1	Score 0	Score 1
Systolic blood pressure	>100 mmHg	≤100 mmHg	≥90 mm Hg	
Respiratory Rate	<22/min	≥22/min	Less than 25 breaths/min	25 breaths/min or greater
Altered mentation	Alert	Altered mentation	Alert	Not alert

Fig. 1: Hour 1 bundle upon recognition of sepsis and septic shock



Lab findings

Increase in lactate dehydrogenase and low platelet are associated with gestational thrombocytopenia. C-reactive protein is increased in pregnancy and the values are further elevated in labor. Albumin is decreased in pregnancy, whereas aspartate aminotransferase and aminotransferase are usually <30 mg/dl. Elevation in fasting serum glucose is estimated to be <90 mg/dl and 2 hours postprandial glucose is <120 mg/dl. Increased D dimer levels and reduced creatinine have been noted in pregnancy. Serum lactate should be measured within six hours of suspicion of severe sepsis and any relevant imaging studies should be performed promptly to confirm the source of infection.

Treatment

The use of antipyretics in febrile pregnant women is imperative to help prevent intrauterine hyperthermia and possible fetal damage. Paracetamol and aspirin are the commonly used drugs for managing fever during pregnancy. Use of NSAIDs after 30 weeks of gestation is contraindicated. Steroids are usually safe and first trimester corticosteroid use may be associated with a slightly increased risk for cleft lip with or without cleft palate. Maternal antibiotics during pregnancy can alter the gut flora or immunity of the fetus.

Key points

Pyrexia in pregnancy and postpartum is relatively common, and it is paramount to identify whether it is due to pregnancy-related causes. Hyperthermia effects on the fetus need close medical attention, as it can lead to severe fetal malformations or death. Sepsis can be insidious and masked, whereas it can rapidly progress with higher mortality. The medications should be prescribed after weighing the risks and benefits during pregnancy and lactation.

References

1. *Adane F, Mulu A, Seyoum G, Gebrie A, Lake A. Prevalence and root causes of surgical site infection among women undergoing caesarean section in Ethiopia: a systematic review and meta-analysis. Patient Safety in Surgery. 2019 Oct 28;13(1):34.*
2. *Al-Riyami N. De Swiet's Medical Disorders in Obstetric Practice. Sultan Qaboos Univ Med J. 2011 Feb;11(1):136–7.*
3. *Sepsis in Pregnancy, Bacterial (Green-top Guideline No. 64a) [Internet]. Royal College of Obstetricians & Gynaecologists. [cited 2021 Feb 27]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg64a/*
4. *SCCM | Adult Patients [Internet]. Society of Critical Care Medicine (SCCM). [cited 2021 Feb 27]. Available from:* https://sccm.org/SurvivingSepsisCampaign/Guidelines/Adult-Patients.
5. *Keighley CL, Skrzypek HJ, Wilson A, Bonning MA, Gilbert GL. Infections in pregnancy. Medical Journal of Australia. 2019;211(3):134–41.*
6. *qSOFA (Quick SOFA) Score for Sepsis [Internet]. MDCalc. [cited 2021 Mar 26]. Available from: https://www.mdcalc.com/qsofa-quick-sofa-score-sepsis*

Imaging for fever evaluation

Dr. Balakrishna Shetty

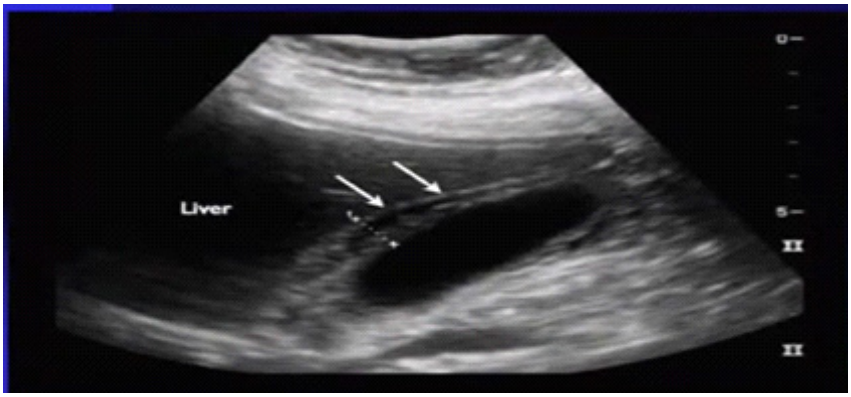
Vice Chancellor, Sri Siddhartha University, Tumakuru, Karnataka
Professor and Consultant in Radiology, ISHA Diagnostics, Bangalore
Member, Consortium Universities for Global Health (CUGH), Washington DC.

Introduction

For the optimal management of fever, imaging plays a crucial role in early diagnosis and exclusion of infection and inflammation. The imaging modalities include structural imaging, microscopic imaging, functional imaging, and inflammation imaging. X-rays, contrast studies, ultrasound, nuclear medicine, angiography, computed tomography, magnetic resonance imaging (MRI), single-photon emission computerized tomography, positron emission tomography, computed tomography, and magnetic resonance-positron emission tomography are the commonly used imaging techniques. The present paper discusses case studies highlighting the significance of imaging in fever evaluation.

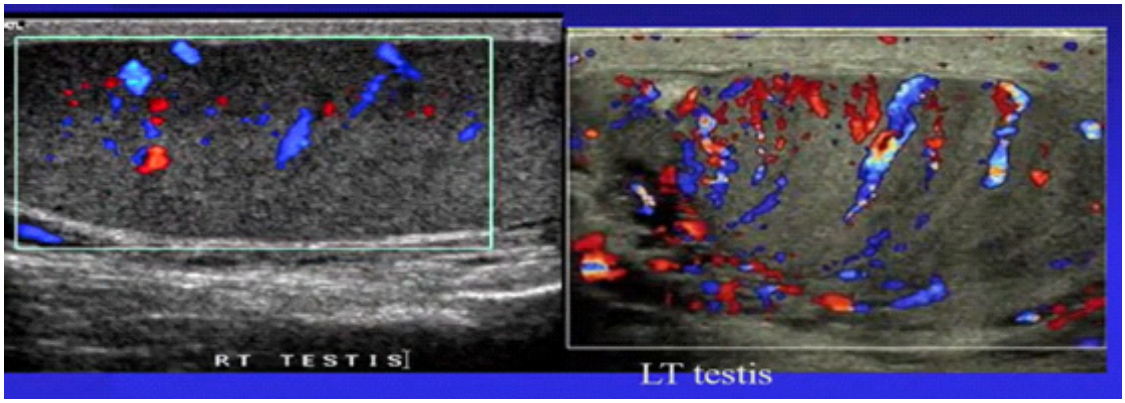
Case 1: An 18-year-old male presented with fever and abdominal pain. Ultrasound of abdomen (Fig. 1) revealed distended gallbladder and small amount of fluid, and based on the imaging, the disease was identified as acalculous cholecystitis. Cholescintigraphy nuclear scan is recommended in cases with uncertainty in diagnosis. The differential diagnosis to be considered are cholangitis, acute cholecystitis, pancreatitis, hepatitis, and other abdominal infections.[1] It is also important to differentiate gall bladder edema from a non-infective condition.

Fig. 1: Ultrasound of abdomen revealing acalculous cholecystitis



Case 2: A 12-year-old boy presented with fever and left testicular pain. Color Doppler revealed lot of vascularity in left testis (Fig. 2) and the diagnosis was concluded as epididymo-orchitis. Doppler ultrasound is the modality of choice for differentiating inflammatory conditions from testicular torsion.[2] In patients presenting with fever and testicular pain and if the color Doppler is revealing absence of flow, it can be considered as a case of testicular torsion.

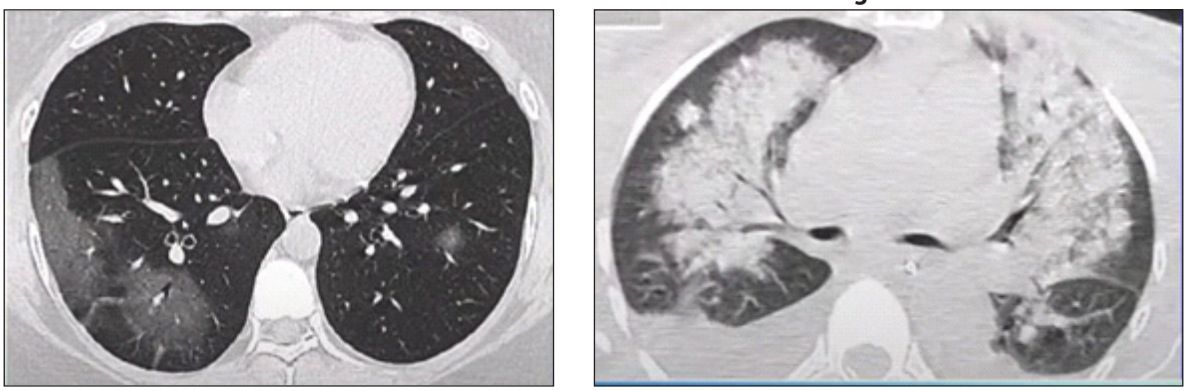
Fig. 2: Color doppler study of testis



Case 3: High-resolution computed tomography (HRCT) of chest conducted for a 55-year-old man presented with fever revealed alveolar edema or ground glass edema and lesions. The diagnosis was concluded as COVID-19 (Fig. 3A). The study highlights the importance to differentiate between cardiogenic edema and viral infection (Fig. 3B). Ground glass density in viral infection is subpleural, whereas it is perihilar in cardiogenic edema. In COVID-19 infection, it generally begins from the peripheral region, whereas, it starts from centre in cardiogenic edema. The presence of hematogenous tiny hard nodules assist in diagnosing miliary tuberculosis. High-density nodules indicate silicosis and large nodules suggest metastatic disease. HRCT should be considered only in diffuse lung infection and interstitial lung disease. Routine CT is ideal for diagnosing metastatic and solid lesions.

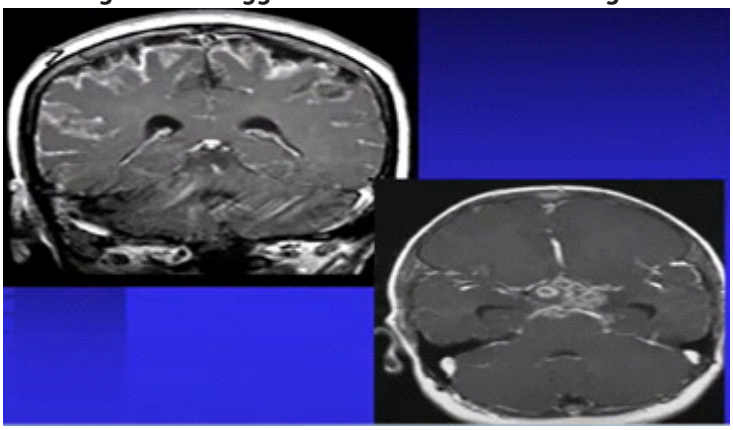
Fig. 3: HRCT of chest differentiating viral infection from cardiogenic edema

A: COVID-19 **B: Cardiogenic edema**



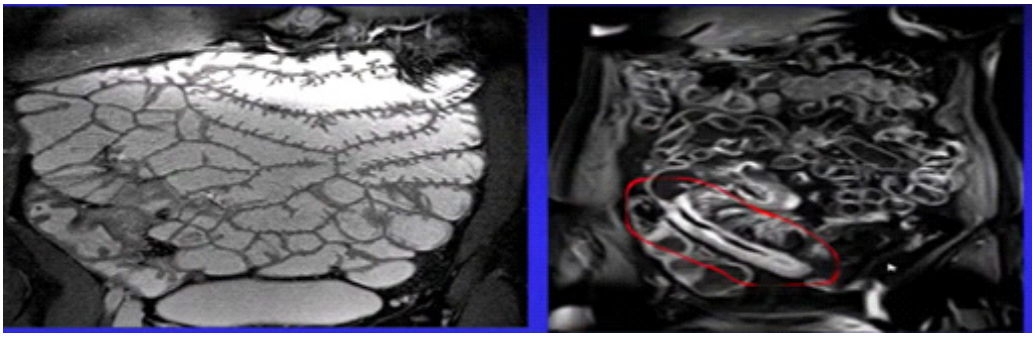
Case 4: A 38-year-old female presented with headache and fever. MRI revealed meningeal enhancement and the diagnosis was concluded as tuberculous meningitis (Fig. 4). Neuroimaging plays a paramount role in the early and accurate diagnosis of tuberculous meningitis and associated complications.[3]

Fig. 4: MRI suggestive of tuberculous meningitis



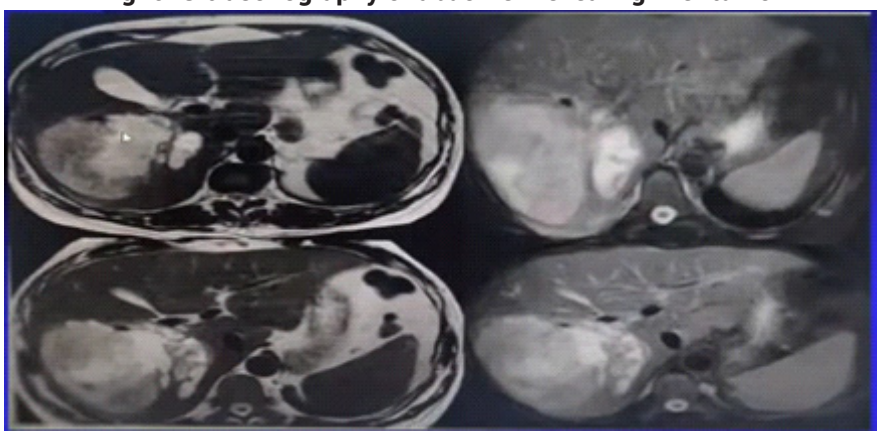
Case 5: A 48-year-old female presented with abdominal pain and fever. MR enteroclysis revealed enhanced bowel loop and diagnosed it as intestinal tuberculosis (Fig. 5). MR enteroclysis assists in the work-up of small-bowel diseases and it is superior over other techniques in combined visualization of luminal, mural, and extramural abnormalities.[1]

Fig. 5: MRI enteroclysis indicating intestinal tuberculosis



Case 6: A 65-year-old patient with abdomen pain and fever. Ultrasonography detected lesions in the right lobe of liver, which was concluded as liver tumor (Fig. 6). Diffusion weighted imaging in imaging of patient with fever is important. Restriction of diffusion of water molecules in intercellular space due to infection leads to water remaining in tissue for longer time causing strong signal. Diffusion-weighted magnetic resonance imaging creates images from the resulting data that uses the diffusion of water molecules to generate contrast in magnetic resonance images. Diffusion weighted imaging determines Apparent diffusion coefficient and image intensity and differentiate between Transudate and exudate.

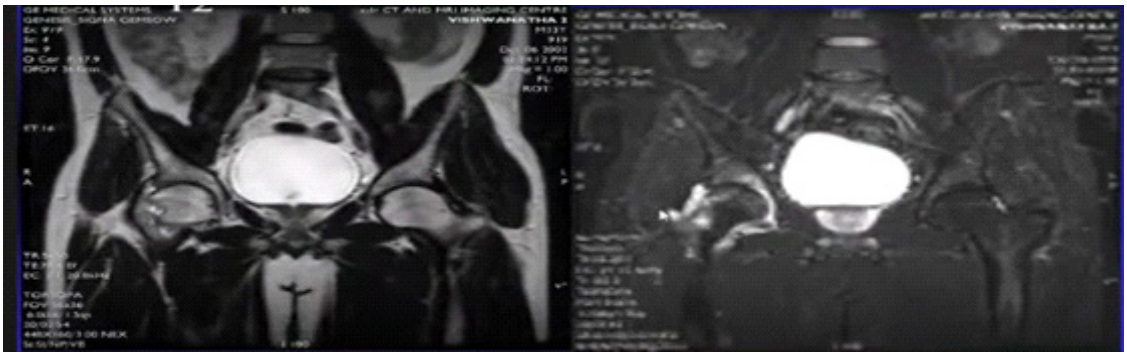
Fig. 6: Ultrasonography of abdomen revealing liver tumor



Case 7: An 18-year-old man presented with right hip joint pain. MRI and fat suppression sequence revealed fluid in right hip. Diffusion-weighted concluded the diagnosis as septic arthritis (Fig. 7).

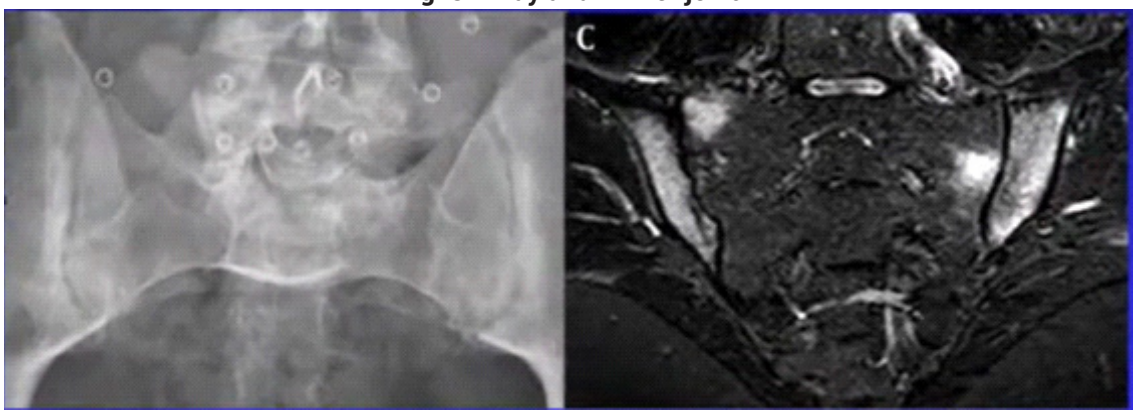
Restricted diffusion of water molecules in intercellular space due to infection leads to prolonged water retention in tissues causing strong signal. Diffusion-weighted MRI assists in generating signal contrast based on the differences in Brownian motion. Diffusion-weighted imaging creates apparent diffusion coefficient and image intensity, thereby to differentiate between transudate and exudate.

Fig. 7: MRI and fat suppression sequence of the right hip



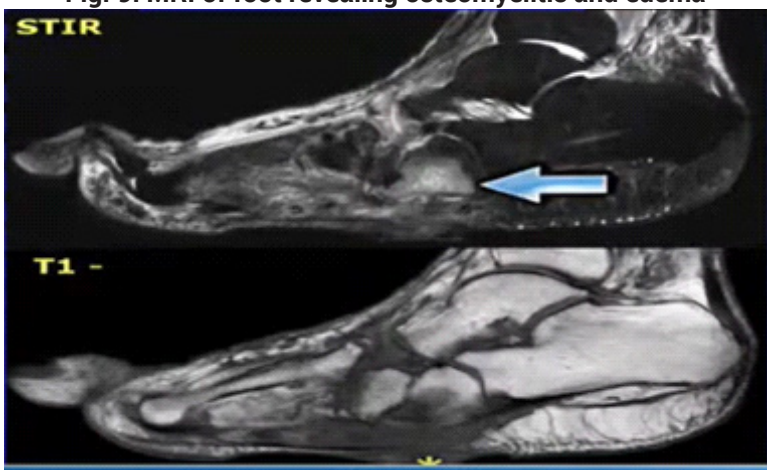
Case 8: A 32-year-old female presented with chronic back pain with intermittent fever. X-ray, MRI and fat suppression revealed stenosis and edema around sacroiliac joint (Fig. 8). There was no restricted diffusion and the diagnosis was concluded as spondyloarthropathy.

Fig. 8: X-ray and MRI of joint



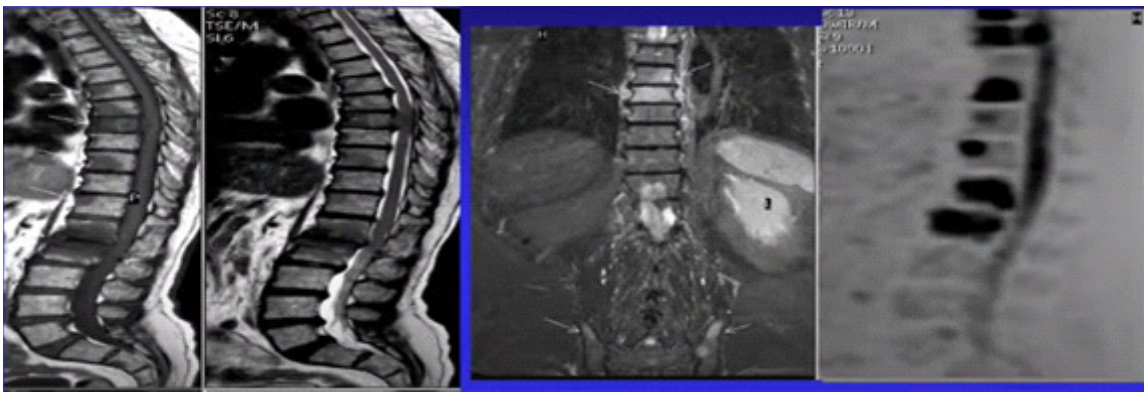
Case 9: A 65-year-old male presented with diabetic foot, ulcer, and fever. MRI of foot revealed inflammation, cellulitis with osteomyelitis and edema (Fig. 9). In diabetic foot, advanced MRI and multi-parametric protocols help in treatment decision making and improved patient outcomes.

Fig. 9: MRI of foot revealing osteomyelitis and edema



Case 10: A 75-year-old female presented with long-standing fever**,** MRI revealed multiple vertebral lesions and the disease was concluded as multiple myeloma (Fig. 10). Bone marrow evaluation with MRI offers benefits beyond morphological information in patients with multiple myeloma.[4]

Fig. 10: MRI of vertebrae revealing multiple vertebral lesions



Conclusion

CT and MRI are relatively new imaging modalities with greatest potential to detect present pathology or predict patient outcomes. Advancements in medical imaging modalities may assist in providing personalised treatment and optimal care in the public health and preventive medicine settings.

References

1. *Jones MW, Ferguson T. Acalculous Cholecystitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Mar 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459182/*
2. *Agrawal AM, Tripathi PS, Shankhwar A, Naveen C. Role of Ultrasound with Color Doppler in Acute Scrotum Management. J Family Med Prim Care. 2014;3(4):409–12.*
3. *Wiarda BM, Kuipers EJ, Heitbrink MA, van Oijen A, Stoker J. MR Enteroclysis of Inflammatory Small-Bowel Diseases. American Journal of Roentgenology. 2006 Aug 1;187(2):522–31.*
4. *Dutoit JC, Verstraete KL. MRI in multiple myeloma: a pictorial review of diagnostic and post-treatment findings. Insights Imaging. 2016 May 10;7(4):553–69.*

Antibiotic stewardship workshop

Dr. Bhaskar Shenoy
Head - Department of Pediatrics
Chief, Division of Pediatric Infectious diseases,
Manipal Hospitals, Bangalore, India

Introduction

The antibiotic resistance has been attributed to the overuse and misuse of antibiotics in daily clinical practice. With increasing antibiotic resistance and limited number of newer antimicrobial drug being available in pharmaceutical industry, antibiotic stewardship is the need of the hour to prevent the antibiotic resistance and optimize patient outcomes.

Antibiotic prescription

While prescribing antibiotics, it is paramount to consider the need of prescription, choice of most appropriate antibiotic and regimen, and ways to monitor antibiotic efficacy. The choice of antibiotic should be mainly determined by source or focus of infection (whether the infection is viral or bacterial, community acquired or nosocomial), patients age and immunologic status.

Case 1: A 5-year-old boy was admitted with fever and cough for eight days. His WBC count was 23,000/cmm and the treatment was started with ceftriaxone and amikacin, in view of the occurrence of lower zone pneumonia in chest X-ray. Since the condition was not improving, the antibiotics were substituted with meropenem for 3 days. Streptococcus is the commonest pathogen noted in infants with community-acquired lobar pneumonia. After ruling out the possibility of causative organisms other than streptococcus, the patient was treated with amoxicillin. The chest X-ray appeared normal after one week of treatment. The case highlights the importance of analyzing the possible etiological agent and best narrow spectrum drug for treatment.

Case 2: An 8-month-old male child was presented with fever and vomiting for 2 days, followed by brief seizures. Physical examination revealed that the child was sick, irritable, and febrile. The child was admitted 15 days back with fever and high CRP, and was treated with piperacillin and tazobactam.

The antibiotic was subsequently upgraded to meropenem, which led to improvement in CRP. However, after 2 days, there was elevation in CRP level and persistence of fever. MRI of brain concluded the diagnosis as meningitis. The child was subsequent treated with ceftriaxone for 10 days and the condition improved after one month of follow-up.

Ceftriaxone is the preferred drug for managing such cases and vancomycin is considered as an add-on to treat ceftriaxone-resistant *Streptococcus pneumoniae*. Verghese et al. reported increasing penicillin resistance and cefotaxime non-susceptibility to pneumococcal meningitis.[1] Ceftriaxone has good antibacterial activity, tolerability at higher dosage, CSF penetration and maintenance of drug level due to non-metabolization in CSF. Whereas, amikacin has poor antibacterial activity against common organism and CSF penetration. In case of ceftriaxone along with sulbactam, organisms causing meningitis do not produce beta-lactamase, hence sulbactam has a poor antibacterial activity and CSF penetration. Cefoperazone has poor CSF penetration. Meropenem is reserved for cefalosporin-resistant organisms and severe polymicrobial organisms. In young infants of 1-3 months, cefotaxime should be used instead of ceftriaxone, and ampicillin 200 mg/kg/daycan also be given. The duration of antibiotic for bacterial meningitis due to *Streptococcus pneumoniae* is 10-14 days, for *Hemophilus influenzae* 7-10 days and *Neisseria meningitidis* 4-7 days.

Case 3: A one-and-half-month-old boy of an HIV-infected mother was presented with right femoral osteomyelitis on day 8 of life. Evaluation of pus culture identified *methicillin-resistant Staphylococcus aureus* (MRSA). The child recovered following treatment with linezolid for 14 days. However, swelling over right femur and left elbow recurred and the diagnosis was concluded as osteomyelitis of femur and upper end of radius. *Staphylococcus aureus* is responsible for >80% of childhood osteomyelitis and there is an increased incidence of community-acquired MRSA. The child was treated with vancomycin along with clindamycin for 3 weeks.

Case study 4: A 20-days-old neonate, admitted to NICU due to respiratory distress, was on ventilator for 8 days. Feed was started on day 17th and the child was septic. Blood culture identified pseudomonas and umbilical catheter culture identified enterococcus, and was started on meropenem and linezolid. For penicillin-resistant enterococcus, vancomycin is the ideal drug. Whereas, linezolid can be used for vancomycin-resistant organisms.

Case 5: A 9-year-old girl, diagnosed with multiple tuberculoma, was started with isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) (HRZE) and steroids. Culture of TB after six weeks showed resistance to H and S and treatment was shifted to R and E. After 14 days, the child had vomiting and MRI showed increase in basal exudates. The drug resistant-TB regimen should be comprised of four drugs and the first-line effective drugs should be continued as further treatment.

Case 6-7: A 11-month-old child was presented with sudden onset of fever and vomiting at onset of illness, followed by watery loose motions for last 2 days. The treatment was started with ofloxacin-ornidazole combination. Since watery diarrhoea is a viral infection, prescription of antibiotic was not appropriate in the case. A 2-year-old boy was presented with cough and watery nose for one month with 102^{0}F fever. The parents had similar symptoms and was started with cefpodoxime. Antibiotic treatment was not required in this case, since watery nose is a viral symptom. An IVF baby, born at 36 weeks through lower segment C-section with no risk factors, was prescribed with IV Cefotaxime

and amikacin as prophylaxis. However, the baby returned with sepsis due to ESBL producing *E.coli*.

Case 9-10: A 18-month-old neonate, presented with fever, irritability, and red bulging eardrum, was diagnosed with acute otitis media. Though the child was prescribed with Amoxiclav at correct dose, due to the occurrence of diarrhea, the parents reduced the dosage without consultation. This in turn led to the development of resistance. Fever persisted with convulsions and CSF culture demonstrated *β lactamase-producing H influenzae*, suggestive of meningitis. The child was started with cefotaxime and amikacin. This child's condition improved after 9 days and was discharged on oral antibiotics upon parent's request. However, the children returned after 1 month with brain abscess due to ESBL producing *E.coli*. These two cases highlight the need for receiving antibiotics at correct doses to prevent resistance.

Case 11-12: A 24-month-old baby presented with refusal to feed, fever for last 24 hours, and hypothermic limbs. In another case, a 2-year-old boy, who was receiving treatment for acute lymphoblastic leukemia, presented with Hb 8%, TLC 1080/mm, ANC of 204/mcL and fever. In both the cases, it is important to start antibiotic immediately, prior to further evaluation, due to the increased susceptibility to bacterial infection in such immunocompromised patients.

Case 13-16: A 4-year-old girl presented with submandibular swelling and acute suppurative lymphadenitis. In another case, a 2-year-old boy presented with high fever for 2 days and bacillary dysentery. A 2-and-half-year-old boy, who presented with cough, fever for 3 days, and breathlessness for one day, was identified as a classic case of pneumonia. A 5-year-old sick-looking child presented with fever, poor appetite, coated tongue, and soft hepatosplenomegaly. Antibiotic treatment is needed in all the aforementioned cases.

Case 17: A 2-year-old boy presented with fever for 2 days and pain on passing urine, and routine test revealed pus cells 40-50. Antibiotic should be started in such case, as there is a high probability of bacterial infection, and appropriate investigation is required.

Case 18: A 5-year-old girl presented with progressive fever, severe anorexia, occasional vomiting, and soft hepatosplenomegaly. Further investigations revealed Hb 12.2 gm%, WBC 6200/mm^3, and neutrophil 68%, and was started on ceftriaxone. Culturing revealed *S. typhi*, which was sensitive to ceftriaxone, azithromycin, and resistant to quinolones. Azithromycin was added to the regimen. In such cases of enteric fever, ceftriaxone may take 5-7 days to show drug actions and no other drug should be added to it. The use of two or more antibiotics is advisable only in case of serious bacterial infections and mixed infection to delay development of resistance and true synergy.

Take home message

- It is important to document a diagnosis and the need of an antibiotic should be evaluated.
- Evaluating the culture, probable resistance, and severity of the infection is paramount.
- Choosing of narrow spectrum agent and administering at right dose and duration are important.
- Review should be conducted at 48 hours, depending on response to therapy and results of culture.
- Optimization, de-escalation and, cessation of treatment should be considered based on the scenarios.

Antibiotic stewardship workshop

Dr. Suresh Kumar
Senior Consultant, Infectious Disease,
Apollo Hospitals, Chennai

Introduction

Antibiotic selection procedure involves the appropriate selection of patient, antibiotic, dose, and duration.[2] Antibiotic should be considered if a patient has septic shock, rapidly deteriorating condition, and possible etiology for bacterial infection. However, it should be started only after sample investigation. If the patient is stable, the prime focus should be on diagnosis before prescribing antibiotic.

Case 1: A 65 years old male with poorly controlled type 2 diabetes presented with 5 days of fever, body pain, sore throat, and minimal cough. However, there was no shortness of breath, dysuria, lower abdomen pain, and hematuria. Urine routine was normal and did not show any pus cell. In such cases, symptomatic treatment is needed, instead of antibiotics.

Case 2: A 45-year-old female, without any comorbid condition, was presented with shortness of breath, tachycardia, and pus cells in urine routine. The patient was febrile and hypotensive. Routine diagnosis can be septic encephalopathy and close differential diagnosis can be meningitis, urosepsis and scrub typhus. Hence antibiotic therapy is needed in this case.

Case 3: A 32-year-old male was presented with 9 days of fever, right sided-headache, purulent nasal discharge from right side, and tenderness over right maxillary sinus. Although the patient was initially treated with paracetamol, the symptoms recurred. X-ray revealed haziness in maxillary sinus. Antibiotic treatment is necessary in the current patient, as routine diagnosis showed sinusitis.

Case 4: A 72-year-old male presented with fever, chills, dysuria for 4 days, vomiting, no bowel disturbances, and stable vitals. Since the urine routine showed pus cells and urine culture showed >1,00,000 colonies, the diagnosis was concluded as urinary tract infection. Upper urinary tract infection can be due to pyelonephritis or prostatitis, which can cause fever, chills, vomiting, dysuria, hematuria

and abdominal pain. Whereas, lower urinary tract infection can be due to cystitis or urethritis, which can cause dysuria, urgency to urinate, hematuria and suprapubic pain. Since the upper urinary tract is involved in the current case, meropenem is an ideal antibiotic.

In order to choose an antibiotic, it is important to know the syndromes and the causative organisms. For example, meningitis is usually caused by Gram-positive organisms and urinary tract infection by Gram-negative organisms. It is important to understand whether the antibiotic spectrum covers the causative organism. For example, although penicillin is a good antibiotic for Gram-positive organisms, it has minimal cover for Gram-negative bacteria and anaerobic organisms. Whereas amoxicillin-clavulanic acid covers Gram-positive, Gram-negative and anaerobic organisms. It is important to consider the antibiotic spectrum whether it is narrow or broad and its coverage for Gram-positive or negative organisms. The common antibiotic spectrums based on the causative organisms are described in table 1 and 2.

Table 1 & 2: The antibiotic spectrum based on the causative microorganisms

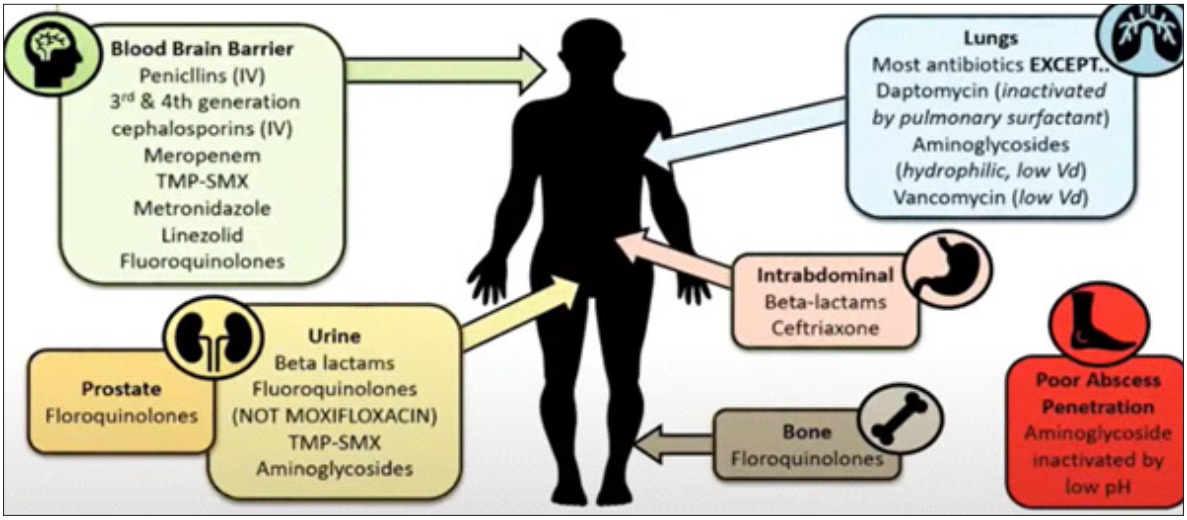
Gram-positive agents	Gram-negative agents	Both Gram positive and negative organisms	**Anaerobic cover**
Older penicillin (CP, Clox)	3rd and 4th generation cephalosporins	Amox-clav, Ampicillin	Amox-clav
1st and 2nd generation cephalosporins	Aztreonam	3rd and 4th generation cephalosporins	Clindamycin
Clindamycin	Cefap-Sul, Pip tazo	Tetracycline	Metronidazole
Linezolid	Carbapenem	Cipro, Levoflox	Cefap-Sulb, Piptazo
Moxifloxacin	Ciprofloxacin and Levofloxacin	Co-trimoxazole	Carbapenem
		Fosfomycin	Tige, Minocycline

	GNR	GPC	Metabolism	Comments
Ciprofloxacin	***	*	Renal	Preferred for GU infections; poor *Strep pneumo* coverage
Levofloxacin	**	**	Renal	Preferred for respiratory tract infections
Moxifloxacin	*	***	Hepatic	No activity vs. *Pseudomonas*

GNR = gram negative rods; GPC = gram positive cocci; relative activity denoted by number of *

The preferred antibiotics based on the site of infections are depicted in figure 1.

Fig. 1: Antibiotics and site of infections



Case 5: A 28-year-old obese male, who was staying in a hostel, presented with fever, constipation for 10 days, and abdominal discomfort. Similar febrile illness, which occurred twice in the last two months, subsided with ciprofloxacin. Further examination revealed palpable spleen, and blood culture revealed *Salmonella typhi*. The diagnosis was considered as typhoid. Since the antibiotic choice depends on local resistance pattern, the choice should be either IV ceftriaxone or azithromycin, and combination drugs should not be considered. Since the patient is obese, the dose should be adjusted based on body weight.

Case 6: A 55-year-old male with type 2 diabetes mellitus presented with fever, cough, and shortness of breath for 3 days. Further examination revealed tachypnea, rales, elevated WBC count, and right lower zone consolidation in chest X-ray. Sputum test revealed streptococcus pneumonia and ideal duration for antibiotic treatment is 5 days.

Case 7: A 60-year-old obese male, with diabetes and coronary artery disease, was planning to undergo coronary artery bypass graft surgery and aortic valve replacement. The patient was a febrile with no fever or dysuria, and stable vital. Urine routine revealed 3-4 pus cells and urine culture revealed klebsiella. The diagnosis was concluded as asymptomatic bacteriuria. It is recommended to use antibiotics to treat asymptomatic bacteriuria in case of pregnancy and before urological surgery.

Case 8: A 52-year-old female with type 2 diabetes planning for root canal was prescribed with Amoxclav plus metronidazole prior to the procedure. However, the patient returned with diarrhea. According to American association of endodontists, antibiotic therapy prior to dental procedures is needed only for patients who used prosthetic cardiac valve or prosthetic material for cardiac valve repair, and those who had infective endocarditis or congenital heart disease.[3]. In the present case, antibiotic was not necessary prior to root canal surgery, and if need, single dose of antibiotic, one hour prior to the procedure, can be prescribed.

Case 9: A 20-year-old man who had undergone open reduction internal fixation presented with swelling. and pain. The pain subsided following IV linezolid treatment, and the oral linezolid was continued for next 3 weeks. The patient returned with wound, pallor, irritation in tongue and weakness. The diagnosis revealed implant-associated osteomyelitis, which is a skin and soft tissue infection caused by Gram-positive organisms. Linezolid is a good Gram-positive antibiotic. However, if the patient's condition is not improving even after prescribing the right antibiotic, addition of newer drug is not the recommended strategy. The solution is source control, and in the present case, it is important to drain the pus. It is also important for a clinician to know the side effects of the drugs. In the current case, linezolid can cause myelosuppression, peripheral neuropathy, dark pigmentation in tongue, and lack of appetite. Hence it is ideal to stop the antibiotic and send the tissue for further evaluation.

Key points

- The appropriate antibiotic should be chosen based on the causing organism, pharmacokinetics, and resistance pattern.
- The dose of antibiotic should be adjusted based on the body weight for a minimum duration of 5-7 days.

References

1. *Verghese VP, Veeraraghavan B, Jayaraman R, Varghese R, Neeravi A, Jayaraman Y, et al. Increasing incidence of penicillin- and cefotaxime-resistant Streptococcus pneumoniae causing meningitis in India: Time for revision of treatment guidelines? Indian Journal of Medical Microbiology. 2017 Apr 1;35(2):228.*
2. *Tamma PD, Miller MA, Cosgrove SE. Rethinking How Antibiotics Are Prescribed: Incorporating the 4 Moments of Antibiotic Decision Making Into Clinical Practice. JAMA. 2019 Jan 15;321(2):139.*
3. *AAE Guidance on Antibiotic Prophylaxis for Patients at Risk of Systemic Disease, 2017, Available from* https://www.aae.org/specialty/publications-research/journal-of-endodontics/

Interpretation of Special Laboratory Investigations in fever

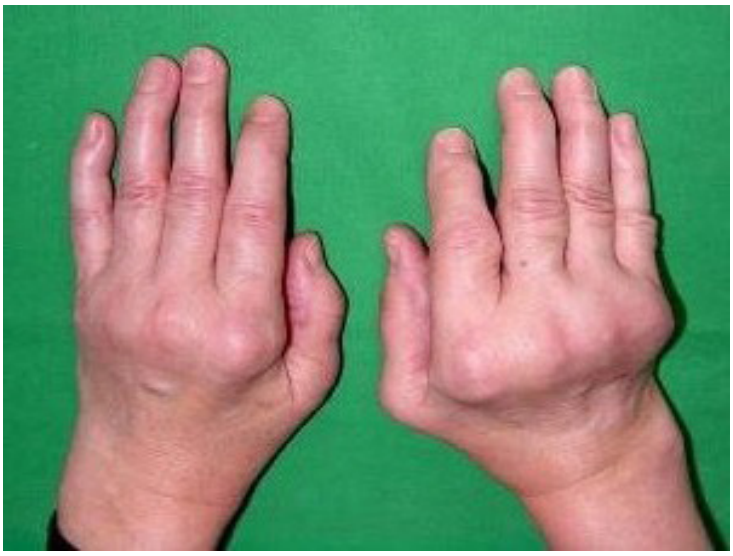
Dr. Ghan Shyam Pangtey*, Nikita Agarwal, Nitesh Bassi****
Corresponding author
Dr. Ghan Shyam Pangtey
Professor of Medicine, Lady Hardinge Medical College & Asso. Hospitals, New Delhi. India.
*Professor, ** Post Graduate student

Introduction

Interpretation of laboratory test and appropriate decision making is paramount for early diagnosis and treatment, and good clinical outcome in disease and health. A good history and clinical examination are the backbones for clinical diagnosis for most of the diseases. The diagnosis may not be made during first visit, especially in early course of the disease, as the disease may be in early evolution phase and typical features may be absent at initial presentation. The autoantibody testing in autoimmune diseases may be treacherous in certain cases, as it may appear positive months to years before the onset of disease. On the contrary, all individuals with abnormal autoantibodies may not develop the disease in their lifetime. We will discuss few important tests in brief which are used commonly in medicine practice.

Rheumatoid factor: Rheumatoid arthritis clinically presents with bilateral symmetrical polyarthritis, primarily affecting small joints of hands (**Figure 1**). It is important to exclude the probability of self-limiting undifferentiated arthritis such as post-viral arthritis before making a diagnosis of rheumatoid arthritis. The most commonly used methods for quantifying RF are latex agglutination method by ELISA or by nephelometric assays. Titres above >1:80 are considered positive, although RF can also be seen in 5-10% of healthy population. RF can only help in diagnosis and its level does not change with disease activity and remission. High titers of RF are associated with more aggressive and erosive disease compared to seronegative rheumatoid arthritis. RF helps in diagnosis, when its interpreted with clinical examination and with objective evidence of inflammatory arthritis. However, negative result does not rule out rheumatoid arthritis and 20-30% of rheumatoid arthritis patients test negative for RF.[1]

Figure 1: Severe active arthritis and deformity of hands in rheumatoid arthritis.



Anti-citrullinated peptide antibody (ACPA): It is used for diagnosing RA and the sensitivity is estimated to be around 50-60% at the onset of rheumatoid arthritis and the antibody titre's may increase in up to 85% of rheumatoid arthritis patients later in the course of disease. A recently available second-generation ELISA has claimed to reach 98% specificity for diagnosis of rheumatoid arthritis with 70% sensitivity, thus more useful than rheumatoid factor in diagnosis. ACPAs can be found in around 25-50% of patients with negative RF. ACPAs found in patients with early undifferentiated arthritis and predicts the development of erosive rheumatoid arthritis later in the disease course.[2] ACPA may rarely found to be positive in viral infections, Lyme disease, Graves disease, SLE and Sjogren's syndrome. ACPA test is more specific than RF for diagnosing rheumatoid arthritis (95% vs. 85%) with similar sensitivity (67% vs. 69%). In appropriate setting of inflammatory arthritis, ACPA may still be positive in up to 34% of rheumatoid arthritis patients who may be negative by RF testing.[3]

Anti-nuclear antibody (ANA): Anti-nuclear antibody detects >95% of systemic lupus erythematosus (SLE), however specificity is as low as 50% for SLE. However, ANA positivity is associated with many rheumatologic conditions. ELISA offers the ease of automated assay with little inter-observer difference. However, indirect immunofluorescence (IIF) test is much more sensitive with nearly 30 known nuclear antigen antibody specificities, whereas the ELISA technique identifies only 10-12 antigens.[4] The gold standard method to detect ANA is by indirect immunofluorescent technique using human epidermoid carcinoma cell line. Titres <1:40 are considered as negative, titres between 1:40 to 1:80 as low positive, and titres >1:160 as strongly positive. Bead multiplex is a newer method of ANA testing in which automated flow cytometric immunoassay based on multiplexed fluorescent microspheres and multiple antibodies can be detected in single procedure using multiple antigen beads. Different ANA patterns can be seen in IIF method such as homogenously distributed DNA, presence of centromeres in dividing cells and extractable nuclear antigens speckled throughout

cell. Anti-U1 ribonucleoprotein (RNP) positive antibody test is hallmark for mixed connective tissue disease. Anti-centromere antibodies are associated with systemic sclerosis and crest syndrome, and anti-Ro/SSA and anti-La/SSB antibodies are associated with Sjogren's syndrome. If ANA is negative, SLE panel test should be avoided. ANA positive can also be found in non-rheumatic diseases such as Hashimoto thyroiditis, Graves disease, autoimmune hepatitis, and primary pulmonary hypertension.

Tests for SLE Disease Activity: Differentiation between SLE disease flare and infection are difficult to differentiate and a challenge in a SLE patients, as laboratory tests can be misleading. Erythrocyte sedimentation rate (ESR) and C-reactive protein are raised in both the conditions (SLE Disease and infections) . C3, C4, CH 50 complement levels are decreased in SLE activity, but not in infection. Raised serum Procalcitonin may be helpful in diagnosing bacterial infection. Blood cultures and other culture may help to confirm diagnosis, although SLE flare may be associated with superadded infection.

Acute phase reactants: They are mainly produced by hepatocytes upon stimulation by cytokines. The serum levels of these protein changes by at least 25% in the first week of inflammation. Anti-inflammatory cytokines initiate inflammation and activate liver to produce fibrinogen, serum amyloid A, haptoglobin, C3 and C reactive protein, causing elevation in acute phase reactants such as erythrocyte sedimentation rate (ESR), ferritin and c-reactive protein(CRP). The differences between ESR and CRP are listed in **Table 1**.

Table 1: Difference between ESR and CRP

	ESR	CRP
Method	Simple, inexpensive, difficult to standardize	Semi quantitative and quantitative methods are available
Variable	Age, anemia, large asymmetric, plasma proteins (fibrinogen, alpha 2 macroglobulin, immunoglobulins)	Determined solely by rate of synthesis
Kinetics	Rises after 24-48 hours of tissue damage; subsides with half-life of 4-6 days	Rises 6 hours after tissue damage; Subsides with half-life of 48 hours
Value of test	Integrates the effect of anemia, acute phase response, and immune response; for detecting and monitoring chronic inflammation	Reflects ongoing inflammation; unsuitable for detecting mild inflammation.

Erythrocyte sedimentation rate: Women generally have slightly higher ESR than men. The upper normal limit of ESR in women is half of their age. Hence females of around 70 years of age may have 35mm of ESR without any illness. In rheumatic diseases, ESRs is part of diagnostic criteria for polymyalgia rheumatica and giant cell arteritis. ESRs can be useful in assessing disease activity or

response to therapy for rheumatoid arthritis as they settle down after disease remission.

C-reactive protein: CRP is another commonly used acute phase reactant. It rises and falls more rapidly in association with other acute phase reactants and it does not get affected by anemia, renal failure or other conditions, while ESR get affected in these situations.

Serum ferritin: Normal values for men and women are 24-336 µgrams/L and 11-307 µgrams/L respectively. Serum ferritin**,** recognized as an acute phase reactant and marker of acute and chronic inflammation, is non-specifically elevated in wide range of inflammatory conditions, acute infection, and malignancy. The elevated ferritin in these states reflects increased total body iron storage, although these stores are sequestered and not available for hematopoiesis, widely recognized as anemia of chronic inflammation**.** Still's disease and hemophagocytic syndrome are the two clinical entities with marked elevation of serum ferritin.[5] Elevation in serum ferritin value >5X the normal (1000 ng/ml) is suggestive of adult-onset Still's disease. Low glycosylated ferritin in combination with high ferritin increases the specificity of diagnosing Adult-onset Still's disease by 92.9%.[6]

Anti-Neutrophilic Cytoplasmic Antibody (ANCA): In 1980s, ANCA was first described as being associated with systemic vasculitis. It represents a subgroup of neutrophil-specific autoantibodies. They are commonly directed against azurophil granule proteins myeloperoxidase (MPO) and proteinase 3 (PR3). ANCAs are characteristics of patients with necrotizing vasculitides such as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The cytoplasmic pattern of ANCA (c-ANCA) is due to 29kDa neutral serine protease, protienase 3(PR-3) located within azurophilic granules of neutrophil, and peroxidase positive lysosomes of monocytes. The perinuclear pattern of IIF (p-ANCA) in vasculitis is due to autoantibodies against myeloperoxidase, but commonly directed against other neutrophil cytoplasmic enzymes including elastase, lactoferrin, lactoperoxidase, and lysozyme. ANCA test should not be used as a screening test in non-selected patients group where the prevalence of vasculitis is low. ANCA tests are mostly valuable in clinical situations where ANCA-associated vasculitis is suspected. ANCA is seen in 90%-95% of individuals with generalized granulomatosis with polyangiitis (GPA/Wegener's granulomatosis), 70%-80% of those with limited GPA forms. Cytoplasmic pattern of ANCA(c-ANCA) is mostly associated with granulomatosis with polyangiitis (>90% sensitivity and specificity). Perinuclear pattern of IIF (p-ANCA) is associated with microscopic polyangiitis (60%-70%), Churg-Strauss, inflammatory bowel disease, and certain drug use.

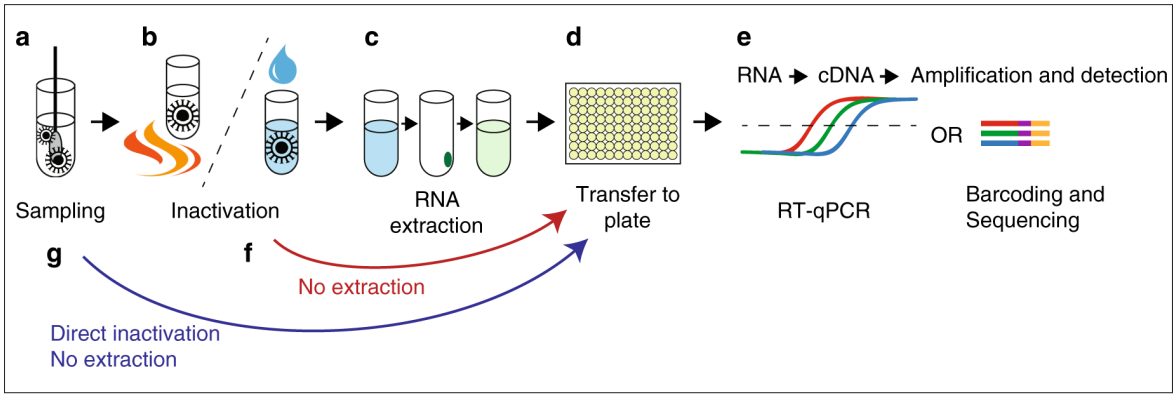
COVID-19 testing

Real-time polymerase chain reaction (rt-PCR), CBNAAT/TRUNAT, rapid antigen test, COVID-antibody test, and neutralizing antibody against spiked protein are the currently available testing methods for COVID-19 or SARS-Cov2 virus disease.

An rt-PCR is based on the detection and quantification of a fluorescent signal (Fig. 2). A cycle threshold (Ct value) is defined as number of cycles required for the fluorescent signal to cross the threshold. Ct levels are inversely proportional to the amount of target nucleic acid in the

sample and in aroutine rtPCR assay, the cycles are repeated/amplified for upto 40 cycles. Ct value <29 indicates strong positive reactions and Ct score of 30-37 are indicative of moderate amount of target nucleic acid. Ct scores of 38-40 are considered as inconclusive rtPCR and test should be repeated after few days. [7]

Figure 2: Overview of SARS-CoV-2 RT-PCR testing procedure



Key points:

- Interpretation of rheumatic test RF/ANCA/ANA complement is challenging and need good knowledge clinical medicine and vast experience in rheumatology.
- ACPA is superior than RF and can be positive in 25%-35% RF negative patients.
- The negative predictive value of ANA is very high.
- PR3-ANCA positive patients have poor prognosis and low response to cyclophosphamide in ANCA-associated vasculitis (AAV) infection.
- Good clinical history and examination are imperative for timely disease diagnosis and better clinical outcome. Laboratory investigations should only be used to support the clinical diagnosis.

References:

1. *Muhlen CA et al. Henrys Clinical Diagnosis and Management by Laboratory methods. 21st ed. McPherson RA, Pincus MR editors, saunders Elsevier; 2007: 916-932.*
2. *Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000 Jan;43(1):155–63.*
3. *Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007 Jun 5;146(11):797–808.*
4. *Handa R. Laboratory investigations in rheumatology: a practical approach. Natl Med J India. 1999 Dec;12(6):285–7.*
5. *Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. Autoimmun Rev. 2007 Aug;6(7):457–63.*
6. *Fautrel B, Le Moël G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol. 2001 Feb;28(2):32*
7. *Smyrlaki I, Ekman M, Lentini A, Rufino de Sousa N, Papanicolaou N, Vondracek M, et al. Massive and rapid COVID-19 testing is feasible by extraction-free SARS-CoV-2 RT-PCR. Nature Communications. 2020 Sep 23;11(1):4812.*

How to work up a viral syndrome when all tests are negative

Dr. Justin Gopaldas
Senior Consultant Intensivist
Manipal Hospital, Bangalore

Introduction

Viral syndrome can be defined as a set of symptoms and signs that are associated with a non-specific or a specific viral illness. Disease-wise estimation has noted that nearly 70% of the outbreaks reported in India are due to viral diseases. A study by Shrestha et al. involving 100 studies on febrile illness has reported that 50% of fever-related diseases in the country are caused by virus.[1]

Symptomatic patient evaluation

First tier-tests are considered for mild viral syndrome with no improvement with 48-hour symptomatic treatment. The choice of tests may depend on settings, basic evaluation, and advanced and tropical work-up. The common tests considered for out-patients are total blood count, inflammatory markers, urine culture and seasonal tests for influenza, COVID-19, dengue, malaria and salmonella. The tests considered for in-patients include total blood count, inflammatory markers, organ-specific tests, urine routine, blood culture, respiratory viral polymerase chain reaction panel, tests for atypical respiratory disease, serology tests and seasonal tests influenza, COVID-19, dengue, malaria and salmonella. The preferred tests for ICU patients include total blood count, inflammatory markers, organ-specific tests, urine routine, multiple culture, respiratory viral polymerase chain reaction panel, tests for atypical respiratory disease, serology tests and seasonal tests for influenza, COVID-19, dengue, malaria and salmonella

Identification after 1st-tier work-up is comparatively low, and it is estimated to be around 40% in community or hospital set-up and 80% in ICU patients. Most of these tests are not as specific and sensitive as diagnostic and screening tools, and false negative reports for four common tropical illness from rapid tests are unacceptably high. Delay from onset of symptoms until the evaluation and

results of 1st work-up contributes to the progression to undifferentiated fever in substantial number of cases, necessitating alternate testing for diagnosis. Second step before repeating the testing involves history review (tropical or non-tropical,) examination of rashes, lymphadenopathy, organomegaly etc, review investigations for microbes and markers, and identification of main- or associated-organs affected by viral syndromes. It is important to consider that further testing should depend on pre-test probability rather than bundle of tests.

Viral syndrome work-up

The first step of viral syndrome work-up is conducting tests for dengue fever and influenza. Second step is based on syndromic approach (e.g. chikungunya virus test for patients with fever and thrombocytopenia), and areas of endemicity (e. g. Kyasanur forest disease test is considered; in patients with fever and acute respiratory distress syndrome). The recommended viral syndrome work-up are listed below:

- Extended respiratory panel test: Fever and acute respiratory distress syndrome
- Fever and liver dysfunction: Hepatitis A, B and C, and repeat test for dengue
- Fever and skin lesions: Measles, varicella-zoster virus, herpes simplex virus and rubella tests
- Fever and CNS manifestations: Tests for herpes simplex virus, rabies and Japanese encephalitis
- Polymerase chain reaction panel test: Fever and multiple organ dysfunction syndrome, Dengue, chikungunya, and hepatitis A or E

Inductive process based on symptom checklist (Fig. 1) is used by doctors who have less experience or experienced doctors who are dealing with unfamiliar problems. Whereas, hypothetico-deductive process (Fig. 2) is used by skilled decision makers. Both are important methods for assessing patients.

Fig. 1: Inductive process based on symptom checklist

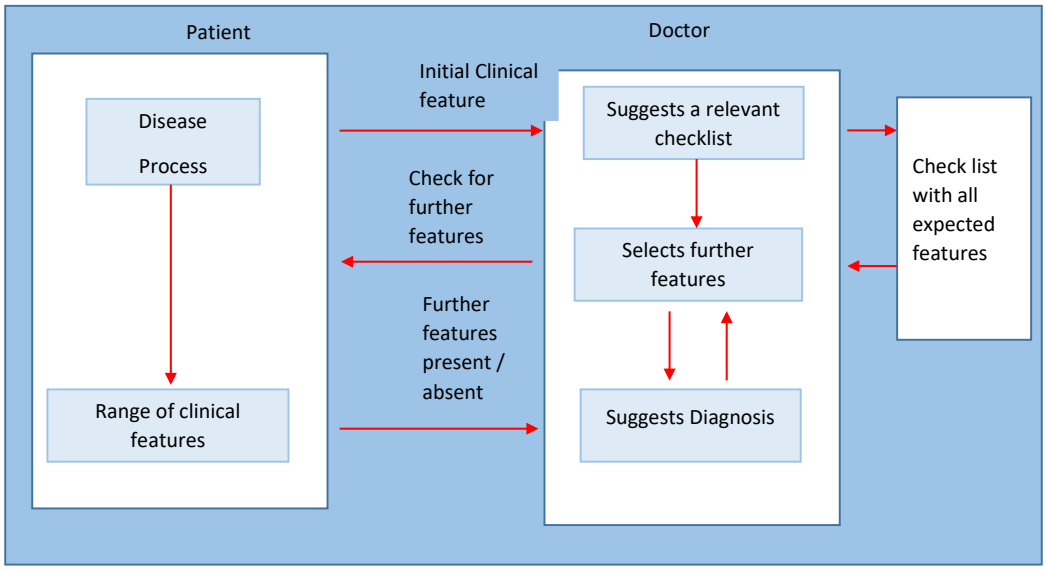
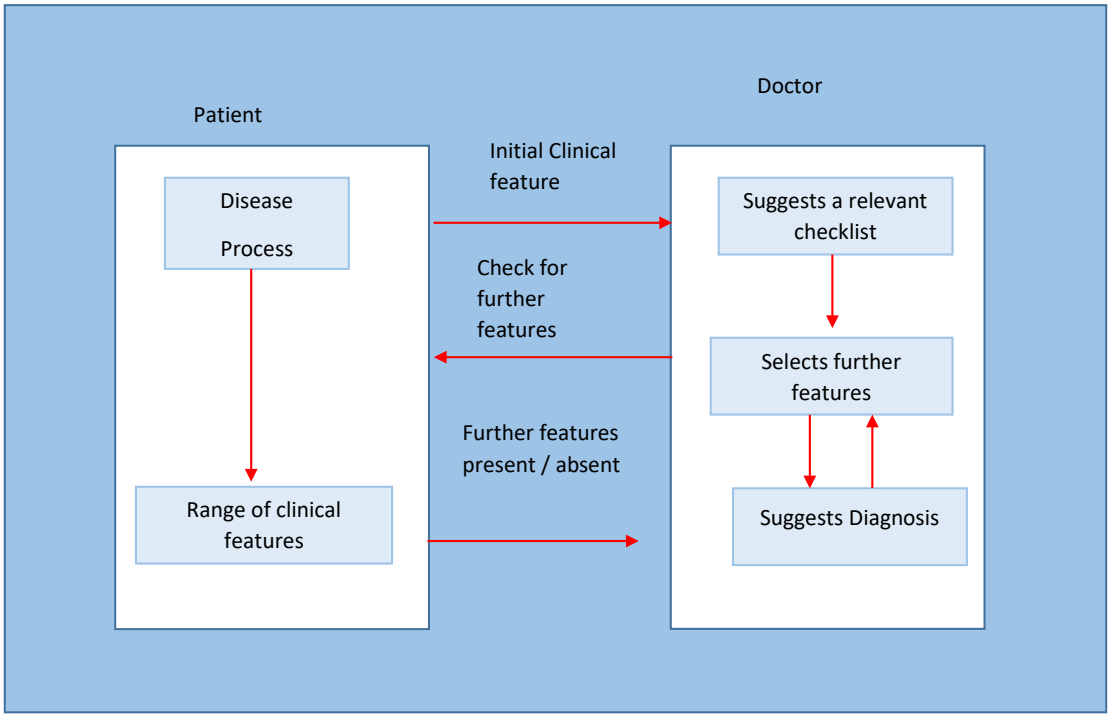


Figure 2: Hypothetico-deductive process



2nd-tier work-up: The 2nd-tier work-up includes repeat culture test, imaging, repeat dengue, malaria, leptospirosis, scrub typhus, and leishmaniasis tests.

3rd- tier work-up: The 3rd-tier work-up includes repeat culture test, imaging, and tests for brucellosis, Q fever, leishmaniasis, schistosomiasis, and trypanosomiasis.

Pyrexia of unknown origin (PUO) work-up: PUO can be defined as fever ≥101˚F documented clinically on several separate occasions and appropriate initial diagnostic work-up of inpatient and outpatient does not reveal etiology.[2] There is significant overlap in illness between third tier and PUO work-up. In Indian settings, the major causes for PUO are infection and extra-pulmonary tuberculosis, whereas pulmonary tuberculosis is not considered as a cause.

Important areas of focus for history, examination, and baseline investigations in PUO are briefed in table 1.[3]

Table 1: Important areas of focus for history, examination, and baseline investigations in PUO

History	Examination	Investigation
Drenching night sweats	Measurement of fever	Full blood count
Weight loss	Lymphadenopathy	Liver function tests
Headache	Scalp tenderness	ESR
Hemoptysis	Hepatosplenomegaly	C reactive protein,
Altered bowel habits, Occupation	Cardiac murmurs	Hepatitis B/C virus, HIV tests
Travel	Respiratory auscultation	Urine/blood cultures
Recreational activities Injecting drug use	Rashes	Antinuclear antibody Rheumatoid factor
Medications		Serum protein electrophoresis Chest X-ray
		Abdominal CT
		Echocardiography

Take home message

- Initial evaluation and Pyrexia of unknown origin evaluation seems to have lot of evidence but there is clear lack of literature about how a physician could focus on step wise evaluation of undifferentiated fever.
- Viral syndrome in India is caused by <40% of viruses and prompts evaluation for zoonotic and non-zoonotic causes.
- Step-wise evaluation assists in clear distinction between steps and guides in the next phase to manage severity and setting of illness.
- Time delay also needs to be considered during the evaluation of difficult to diagnose and undifferentiated fever.

References

1. *Shrestha P, Roberts T, Homsana A, Myat TO, Crump JA, Lubell Y, et al. Febrile illness in Asia: gaps in epidemiology, diagnosis, and management for informing health policy. Clin Microbiol Infect. 2018 Aug;24(8):815–26.*
2. *Hersch EC, Oh RC. Prolonged Febrile Illness and Fever of Unknown Origin in Adults. AFP. 2014 Jul 15;90(2):91–6.*
3. *Beresford RW, Gosbell IB. Pyrexia of unknown origin: causes, investigation, and management. Internal Medicine Journal. 2016;46(9):1011–6.*

Approach to tropical fevers with renal involvement/renal syndromes

Dr. Anirban Ganguli

Attending Nephrologist, Georgetown University/Washington Hospital Center, Washington, DC, USA

Introduction

Tropical fever indicates infections that are prevalent or unique to tropical and subtropical regions. The common infections include dengue hemorrhagic fever, rickettsial infections/scrub typhus, malaria (usually *falciparum*), typhoid, leptospirosis, bacterial sepsis and common viral infections like influenza. The five syndromes of tropical fever are undifferentiated fever, fever with rash or thrombocytopenia, fever with acute respiratory distress syndrome, febrile encephalopathy, and fever with multi-organ dysfunction.[1]

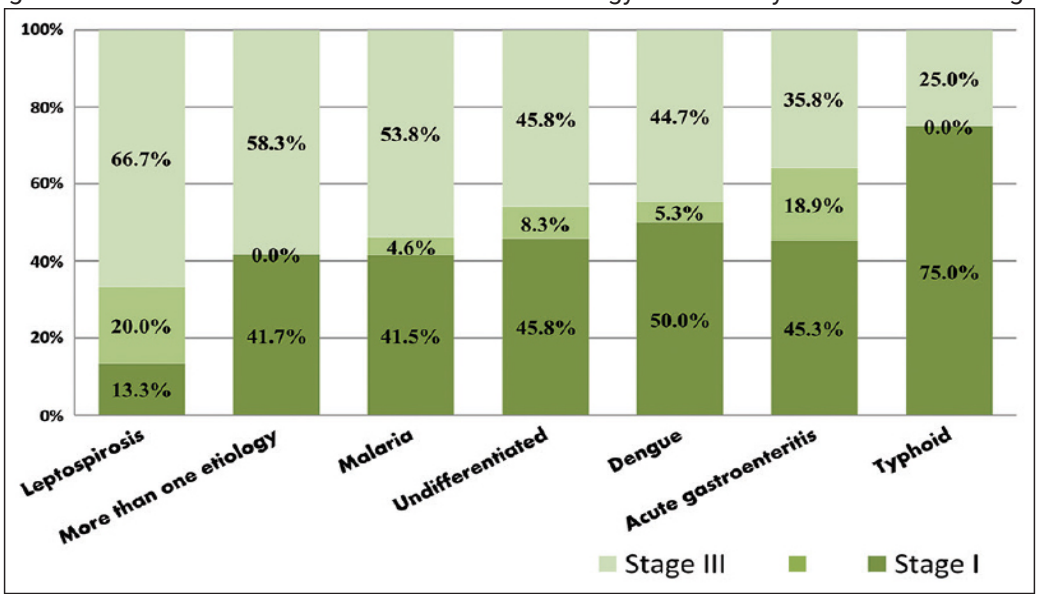
Tropical fever and renal involvement

There are two important studies by Basu et al. and Nair et al on occurrence of acute kidney injury (AKI) in tropical acute febrile illness. These studies have briefed the incidence and severity of AKI based on RIFLE and KDIGO classification, and its association based on mortality and dialysis requirement (Table 1).[2,3] Association between infectious disease etiology and severity of AKI network stages is depicted in figure 1.

Table 1: Severity of AKI and its association with mortality and dialysis requirement

Parameters	Basu et al. (n=367)	Nair et al. (n=600)
AKI incidence	41.1% (RIFLE)	54% (KDIGO)
On admission	35.7%	-
in hospital	7.9%	-
Need of dialysis	19.2%	5.5%
Overall mortality	12.3%	5.5%
AKI mortality	1.6 - 45.3%	0.17-2.5%

Fig. 1: Association between infectious disease etiology and severity of AKI network stages



Mechanism of renal involvement in tropical fevers: Mechanism can be either direct involvement by the pathogen or toxin leading to nausea, vomiting, hypotension, rhabdomyolysis and hemolysis. Nephrotoxic drugs causing acute interstitial nephritis and immunological response to microbial antigen-antibody complex formation can lead to acute or glomerulonephritis.

Prerenal AKI and febrile illness: The common prerenal causes of AKI in tropical fever are diarrhea, vomiting, diuretics, hemorrhagic shock, capillary leak syndrome, distributive or cardiogenic shock, and hypotension. Analgesic combinations such as NSAIDS and ACE inhibitors of drugs can lead to drug-induced acute renal failure.[5]

Sepsis and AKI: Sepsis is the commonest cause of AKI. It is estimated to cause 49 million cases of sepsis, 11 million sepsis-related deaths, and mortality rate of 42% worldwide. One in three patients with sepsis is estimated to have AKI.[6] Patients on dialysis has two-fold increased risk of mortality than non-dialysis patients.[7] Sepsis, as a cause of community-acquired AKI, accounts for 13.9% cases in India and highest in-hospital mortality (46%).[8] There are mainly three processes for pathophysiology, i.e. ischemia, inflammation, and toxic injury to the kidney due to cytotoxic-mediated inflammation.[9]

Myoglobinuric AKI in tropical fever: Myoglobinuric AKI is common in dengue or any other immunogenic fever presenting oliguria and cola-coloured urine. Diagnostic tests reveal hyperkalemia, hyperphosphatemia, hyperuricemia, and elevated aspartate aminotransferase, alanine transaminase, and lactate dehydrogenase.[10]

Hemolysis and AKI: Hemolysis and AKI can be seen in patients with falciparum malaria. General mechanism involves release of parasitized red blood cells (pRBCs). The fraction of non-pRBCs is lower due to RBC deformity and oxidative stress, and the subsequent release of cell-free hemoglobin into the blood and renal tubules causes iron toxicity. Nitric oxide causes renal vasoconstriction leading to acute tubular necrosis. Blackwater fever (BWF) is a severe clinical syndrome, characterized

by intravascular hemolysis, hemoglobinuria, and acute renal failure. It is seen in those exposed to *Plasmodium falciparum* and patients receiving quinine irregularly.[11,12]

Renal and liver involvement in tropical fevers: It could be a simultaneous involvement, as in malaria and leptospirosis, or systematic illness causing multiorgan failure, cytokine storm as in dengue, hantavirus, rickettsiosis, and falciparum malaria. It could be a primary liver involvement leading to the secondary renal involvement, which could be acute viral hepatitis E, acute glomerulonephritis, prerenal azotemia, hepato-renal syndrome, acute tubular necrosis and bile cast nephropathy. These conditions can cause severe AKI. [13, 14]

Acute glomerulonephritis and tropical fever: Acute glomerulonephritis is a rare presentation, and it is immune complex-mediated. It has variable presentations including acute nephritic syndrome, hematuria, variable proteinuria, hypertension, and rapid progressive glomerulonephritis. It can be seen in malaria as plasmodium malaria-associated membrano-proliferative glomerulonephritis.[15] In dengue, it is seen as variable proteinuria with low platelets and mesangial proliferative glomerulonephritis with IgA deposits.[16] In typhoid, it may present as proliferative glomerulonephritis IgG and C3 immune deposits.[17] In case of staphylococcus infection, mesangial proliferative glomerulonephritis with complimentary deposits is noted.[18]

Acute interstitial nephritis in tropical fever: Acute interstitial nephritis in tropical fever is typically seen in leptospirosis, scrub typhus, enteric fever, haemorrhagic fever with renal syndrome, hantavirus and tuberculosis.

Infectious vasculitis in tropical fever: Infectious vasculitis in tropical fever is a prototype of scrub typhus caused by *Orientia tsutsugamushi*. Infectious vasculitis includes skin and multiorgan vasculitis, direct endothelial infection, disseminated intravascular coagulation (DIC), and small vessel vasculitis. In renal biopsy, patchy acute tubular necrosis with acute interstitial nephritis is seen.[19]

Other renal syndromes: Other renal syndromes are seen with tropical fever such as hematuria, protienuria, hypokalemia, hyponatremia, pyelitis, pyelonephritis, cystitis, and chronic kidney disease.

Approach to tropical fevers with renal involvement or renal syndrome: It is paramount to consider the two different aspects i.e the known etiology of tropical fever and a syndrome approach with unknown etiologies. In the first case of known etiology, the primary step is to identify the different risks involved in AKI. Specific risk factors in dengue include male gender, dengue, hemorrhagic fever, rhabdomyolysis, multiple-organ dysfunction, hypertension, diabetes mellitus, delayed hospitalization and use of nephrotoxic drugs.[20] For malaria, the risk factors are hyperbilirubinemia, *P. falciparum* infection, sepsis, and hospital-acquired secondary infection.[21] The risk factors of scrub typhus include underlying CKD, older age, lower serum albumin level and time to hospital presentation after symptom onset.[22] The risk factors for leptospirosis are jaundice, vomiting, Hypotension, leukocytosis, thrombocytopenia and serovar Pyrogenes.[23] For patient already identified with AKI, work-up to differentiate between primary and intrinsic AKI should be followed by stage-based management.

Key points

- Various types of renal involvement have been observed in different tropical fever.
- Renal syndromes originate from multiple mechanisms such as tissue invasion, systematic inflammatory response and toxin-mediated effects.
- AKI in tropical fever indicates severe diseases and needs expeditious management including source control.

References

1. *Singhi S, Chaudhary D, Varghese GM, Bhalla A, Karthi N, Kalantri S, et al. Tropical fevers: Management guidelines. Indian J Crit Care Med. 2014 Feb;18(2):62–9.*
2. *Basu G, Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JAJ, et al. Acute kidney injury in tropical acute febrile illness in a tertiary care centre—RIFLE criteria validation. Nephrology Dialysis Transplantation. 2011 Feb 1;26(2):524–31.*
3. *Nair JJ, Bhat A, Prabhu MV. A Clinical Study of Acute Kidney Injury in Tropical Acute Febrile Illness. J Clin Diagn Res. 2016 Aug;10(8):OC01-05.*
4. *Mehta K, Pajai A, Bhurke S, Shirkande A, Bhadade R, D'Souza1 R. Acute kidney injury of infectious etiology in monsoon season: A prospective study using acute kidney injury network criteria. Indian Journal of Nephrology. 2018 Mar 1;28(2):143.*
5. *Jayakumar M, Prabahar MR, Fernando EM, Manorajan R, Venkatraman R, Balaraman V. Epidemiologic Trend Changes in Acute Renal Failure—A Tertiary Center Experience from South India. Renal Failure. 2006 Jan 1;28(5):405–10.*
6. *Bellomo R, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M, et al. Acute kidney injury in sepsis. Intensive Care Med. 2017 Jun;43(6):816–28.*
7. *Sakhuja A, Kumar G, Gupta S, Mittal T, Taneja A, Nanchal RS. Acute Kidney Injury Requiring Dialysis in Severe Sepsis. Am J Respir Crit Care Med. 2015 Oct 15;192(8):951–7.*
8. *Kaul A, Sharma RK, Tripathi R, Suresh KJ, Bhatt S, Prasad N. Spectrum of community-acquired acute kidney injury in India: A retrospective study. Saudi Journal of Kidney Diseases and Transplantation. 2012 May 1;23(3):619.*
9. *Doi K. Role of kidney injury in sepsis. Journal of Intensive Care. 2016 Mar 23;4(1):17.*
10. *Bosch X, Poch E, Grau JM. Rhabdomyolysis, and acute kidney injury. N Engl J Med. 2009 Jul 2;361(1):62–72.*
11. *White NJ. Anaemia and malaria. Malaria Journal. 2018 Oct 19;17(1):371.*
12. *Brunee F, Gachot B, Wolff M, Regnier B, Danis M, Vachon F, et al. Resurgence of Blackwater Fever in Long-Term European Expatriates in Africa: Report of 21 Cases and Review. Clinical Infectious Diseases. 2001 Apr 15;32(8):1133–40.*
13. *Deepak N A, Patel ND. Differential diagnosis of acute liver failure in India. Ann Hepatol. 2006 Sep;5(3):150–6.*
14. *Mohapatra MK, Behera AK, Karua PC, Bariha PK, Rath A, Aggrawal KC, et al. Urinary bile casts in bile cast nephropathy secondary to severe falciparum malaria. Clinical Kidney Journal. 2016 Aug 1;9(4):644–8.*
15. *Barsoum RS. Malarial acute renal failure. J Am Soc Nephrol. 2000 Nov;11(11):2147–54.*
16. *Lizarraga KJ, Nayer A. Dengue-associated kidney disease. J Nephropathol. 2014;3(2):57–62.*
17. *Buka I, Coovadia HM. Typhoid glomerulonephritis. Arch Dis Child. 1980 Apr;55(4):305–7.*
18. *Satoskar AA, Parikh SV, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. Nat Rev Nephrol. 2020 Jan;16(1):32–50.*
19. *Kim D-Y, Park H-S, Han D-J, Kang H-C, Lee J-H, Jang W-J, et al. A case of scrub typhus requiring maintenance hemodialysis. Kidney Res Clin Pract. 2013 Dec;32(4):190–3.*
20. *Patel ML, Himanshu D, Chaudhary SC, Atam V, Sachan R, Misra R, et al. Clinical characteristic and risk factors of acute kidney injury among dengue viral infections in adults: A retrospective analysis. Indian Journal of Nephrology. 2019 Jan 1;29(1):15.*
21. *da Silva GB, Pinto JR, Barros EJG, Farias GMN, Daher EDF. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017; 59: e53.*
22. *Hwang K, Jang H, Lee T, Cho H seop, Bae E, Chang S-H, et al. Incidence, risk factors and clinical outcomes of acute kidney injury associated with scrub typhus: A retrospective study of 510 consecutive patients in South Korea (2001-2013). BMJ Open. 2017 Mar 1;7:e013882.*
23. *B S, M V, S V. 1481. A Study for Risk Factors of Acute Kidney Injury in Leptospirosis in a Tertiary Health Center in South India. Open Forum Infect Dis. 2019 Oct 23;6(Suppl 2):S540–S540.*

The importance of nutrition in immunity

Dr. A. Muruganathan

Governor - American College of Physicians India Chapter
Past President, Association of Physicians of India, Hypertension Society of India, Past Dean–Indian College of Physicians.

Introduction

Nutrition is the process of food intake and its utilization for growth, metabolism, and repair. Immune system can be defined as integrated body system of organs, tissues, cells, and cell products such as antibodies that help in differentiating self from non-self and neutralize potentially pathogenic organisms and substances. Protein, antioxidants, essential fatty acids, certain vitamins, and minerals are key to a healthy immune system.

Diet and immunity

Eating a low fat, plant-based diet may help in boosting immune system and to reduce inflammatory biomarkers. Vegetarians are reported to have more effective white blood cells, as opposed to non-vegetarians due to high intake of vitamins and low fat intake.[1] Studies have shown that limited dietary fat may help strengthen the immune system functioning. Research has also shown that oil may impair effective white blood cell function and high fat diets may alter the gut microbiota that assist in immune response.[2] Maintaining a healthy weight can also contribute to effective immune system functioning, as obesity is linked to increased risk of influenza and other infections such as pneumonia. Fibre intake may be linked to improved immunity by lowering body mass index.

Protein and immunity

Low protein status can increase the risk of infection by lowering antibody production and decreasing the amount of functional active immunoglobulins. Protein malnutrition and increased susceptibility to Zika and influenza virus are related to cell-mediated immunity and decreased function of neutrophils, complement system, IgA, and antibody response.[3] Protein is crucial for both adaptive and innate immunity, especially for building and repairing body tissues and fighting viral and bacterial infections.

Depending on severity of disease, it is recommended to provide 20-30 kcal/kg/day and daily protein requirement may vary between 1.2 to 2.0 g.[4] It is also helpful in antibody production, and activation of T lymphocytes, B lymphocytes, natural killer cells, and macrophages due to the immunomodulatory properties. Amino acids such as glutamine and arginine are considered as nutrition therapy in pre-surgery patients because their ability to stimulate the immune systems. Deficiency and imbalance of these amino acids can affect the immune response. Most important immunological effects for majority of whey protein are the stimulation of innate immunity via an increase in macrophage activity and IL-8 production. Eggs, shellfish, many vegetables, and grains are also excellent sources of many of the immune-stimulating amino acids.[3,5,6]

Importance of food groups

Grains consist of fibre, vitamins, antioxidants, trace minerals, protein, and carbohydrates. Vegetables contains fibre, vitamins, and minerals. Fruits contain fibre, carbohydrates, vitamins and minerals, especially coloured food like strawberries, cherries, carrots, and tomato contain many beneficial phytonutrients with antioxidants. Meat and beans contain protein, vitamin E and B, iron, zinc, and magnesium. Dairy products contain protein, carbohydrate, calcium, and potassium.

Fibre: Soluble fibre like fructo-oligosaccharides help to improve gut health and immunity. Wholegrains, fresh fruits, and vegetables, are fermented by friendly bacteria in colon to short chain fatty acids (SCFAs), which are used as fuels by gastrointestinal tract cells. Studies have shown that fibres that can produce SCFAs also promote a healthy gastrointestinal barrier.

Herbs to improve immunity: Ginger is known for its anti-inflammatory properties and as a digestive aid to sooth tummy aches. Turmeric is an ancient herb with anti-inflammatory, and anticancer properties with active ingredient curcumin. Amla (*Phyllanthus emblica*) is a richest source of vitamin C and antioxidants to improve immunity. Tulsi (*Ocimum sanctum*) helps in relieving high fever, sore throat, headache, cold, cough, flu, and chest congestion. Ashwagandha (*Withania somnifera*) increases WBC and platelet count, and number of stem cells in the bone marrow, prevents myelosuppression, activates peritoneal macrophages, and reduces stress. Pipalli (*Piper longum*) removes toxins and kapha from lungs and its rejuvenating qualities helps to strengthen immune system.

Almonds: A handful of almonds boosts immune system from the effects of stress and 1/4 cup serving nearly carries 50% of the daily recommended amount of vitamin E, which helps the immune system. Almonds also contain riboflavin, niacin, and vitamin B, which help in relieving stress.

Seeds: Sunflower, pumpkin, and flax seeds are very high in fibre and provide good amount of protein, and healthy omega-3 fatty acids.

Probiotics: Lactobacillus, bifidobacterium and spirulina are nutrient dense food boosting immunity. Low-fat yogurt contains live and active cultures, which may stimulate immune system and it also contains vitamin D.

Fruits: Grapefruits is packed with flavonoids which have been found to increase immune system activation. Watermelon contains antioxidants and glutathione that known to help strengthen the immune system.

Garlic: It offers several antioxidants that battle immune system invaders. Allicin, a compound found

in raw garlic produced from alliin, exhibits important antiviral, antifungal, and antibiotic properties.

Button mushrooms: Button mushrooms contain selenium, antioxidants and are a rich source of zinc. Recent studies have reported that mushroom intake can improve the response of white blood cells.

Tea: Tea contains polyphenols and antioxidants**.** Some components of tea such as epigallocatechin can directly attack invading microbes such as flu and cold viruses, in addition to boost the immune systems.

Lemons: They are a great source of vitamin C and maintain the balance of acids and alkali in body.

Apple cider vinegar: It is a great source of calcium, potassium, magnesium, sodium phosphorus, iron, sulphur, and fluorine.

Fish: Tuna, salmon, and sardines contain omega-3 fatty acids and essential fatty acids are found in cold-water fish. A healthy range of monosaturated fatty acids can also support healthy gastrointestinal cells by promoting healthy membranes.

Omega-3 fatty acids: Diet low in omega-3 fatty acids is associated with chronic inflammatory conditions and autoimmune diseases. Maintaining optimum levels of omega-3 and 6 fatty acids in body can be accomplished by reducing consumption of meats, dairy products, and refined foods, while increasing the intake of cold-water fish, flaxseed oil, walnuts, and green leafy vegetables.

Indian diet

National Nutrition Monitoring Bureau (NNMB) survey indicates that daily intake of food including cereals and millets in Indian household is lower than recommended dietary allowances (RDA). Average consumption of pulse and legumes was 31% lower than RDA and consumption of green leafy vegetables, which are rich sources of micronutrients, are grossly inadequate.[6] Cereal-pulse based Indian diets are qualitatively deficient in micronutrients particularly in Iron, zinc, vitamin A, riboflavin, folic acid, vitamin D etc. Nearly all the vitamins are necessary to maintain and promote some aspect of immune system.[7]

Antioxidants: Reactive oxygen species**,** free radicals and other damaging molecules are generated at sites of infection and inflammation to kill unhealthy cells. However, when antioxidants systems are not functioning or antioxidants are insufficient in diet, these molecules are not disarmed and can cause damages to healthy tissue as well.

Role of vitamins and minerals in immune function

Vitamins and trace elements such as vitamin A, vitamin $B_{6,}$ B_{12}, vitamin C, vitamin D, vitamin E, folic acid, iron, zinc, copper, and selenium support immune function by strengthening epithelial barrier, and cellular and humoral immune responses. Vitamin C decreases the length of time and severity of symptoms associated with upper respiratory viral infections. Vitamin C and E are antioxidants that help in destroying free radicals, and promoting healing at site of inflammation and white blood cell production. Source of vitamin C includes citrus fruits, broccoli, kale, beet greens, asparagus etc. Vitamin E decreases the production of nitrogen oxide, resulting in prostaglandin E2 downregulation and inhibition of cyclooxygenase. Vitamin E sources include nuts, seeds, spinach, and broccoli.

Vitamin B1 and B2 are important for normal antibody response. Vitamin B5 promotes the production and release of antibodies from B-cells. Vitamin B6 deficiency consistently impairs T-cell functioning. Vitamin B12 inhibits phagocytic cells and T-cell function. Folic acid deficiency leads to decrease in T-cells functioning and production of RBCs. Vitamin B6, required for the endogenous synthesis and metabolism of amino acids, has roles in lymphocyte proliferation; maturation and differentiation of NK cell activity antibody production and maintenance of Th1 immune response.[8] Vitamin B12 deficiency leads to compromised cell-mediated and humoral immunity. Supplementation of B12 has been shown to improve immune response in human models.[9] Nicotinamide present in Vitamin B3 increases the downstream antimicrobial targets. Whole grains, vegetables and fruits serve as excellent sources of B vitamins.

Vitamin A deficiency impairs antibody function and T cell activity. Beta-carotene is a powerful antioxidant that can reduce inflammation and boost immune system. Excellent sources include sweet potatoes, carrots, and green leafy vegetables. Vitamin K supports healthy blood clotting and necessary for seclusion of areas of injury in the healing process and the sources include cauliflower and green vegetables. Sources of vitamin A and E are leafy greens, carrots, sweet potatoes, winter squash, asparagus, and bok choy. Vitamin D deficiency correlates with infection rates, sepsis, renal, respiratory failure, and mortality. Food sources of Vitamin D include cereals, plant-based milk and supplements. Zinc antioxidant effects protect against ROS and RNS and helps modulating cytokines release and induces proliferation of CD8+. It also helps maintain skin and mucosal integrity and have central role in cellular growth and differentiation of immune cells.[10] Although excess of zinc also shown negative effects on immune function and can inhibit the phagocytic cells. Hence, maintaining adequate but not excessive levels of zinc is important.[11] Spinach, asparagus, mushrooms, sesame seeds, pumpkin seeds, lentils, cashews, quinoa are excellent sources of zinc. Iron deficiency results in impaired response to antibodies; copper deficiency is associated with an increase in infections and impair development of immune cells such as T cells and phagocytic cells. Selenium and manganese are important for healing and may serve as immunostimulants. Sources of selenium are fish, shellfish, tofu and wholegrain. Sources of copper include Sesame seeds, cashew, soybeans, mushrooms, green vegetables. Spinach, Swiss chard, cumin, turmeric, green vegetables are good sources of iron.

The roles of different vitamins/minerals and the effects of their deficiency are listed in table 1.

Table 1: roles of different vitamins/minerals and the effects of their deficiency

Vitamins/ minerals	Roles	Deficiency effects
Vitamin E	Enhances activity of natural killer cells Maintains cell membrane	Impairs the functioning of cells and B cells
Vitamin A	Maintains the structure and functionality of mucous membranes	Drying of mucous membranes
Vitamin C	Enhances microbial killing Nourishes barriers against pathogens	High susceptibility to infection and inflammation
Vitamin D	Decreases production of inflammatory cytokines Increases production of anti-inflammatory cytokines	Associated with multiple sclerosis and rheumatoid arthritis
Iron	Proliferation and maturation of lymphocytes	Disruption of innate immunity
Folate	Synthesis and repair of protein and DNA	Decreased response of T Lymphocytes
Zinc	Development and functioning of neutrophils	Hampered functioning of antibodies and white blood cells
Selenium	Enhances T-lymphocyte immune response	Less robust immune response

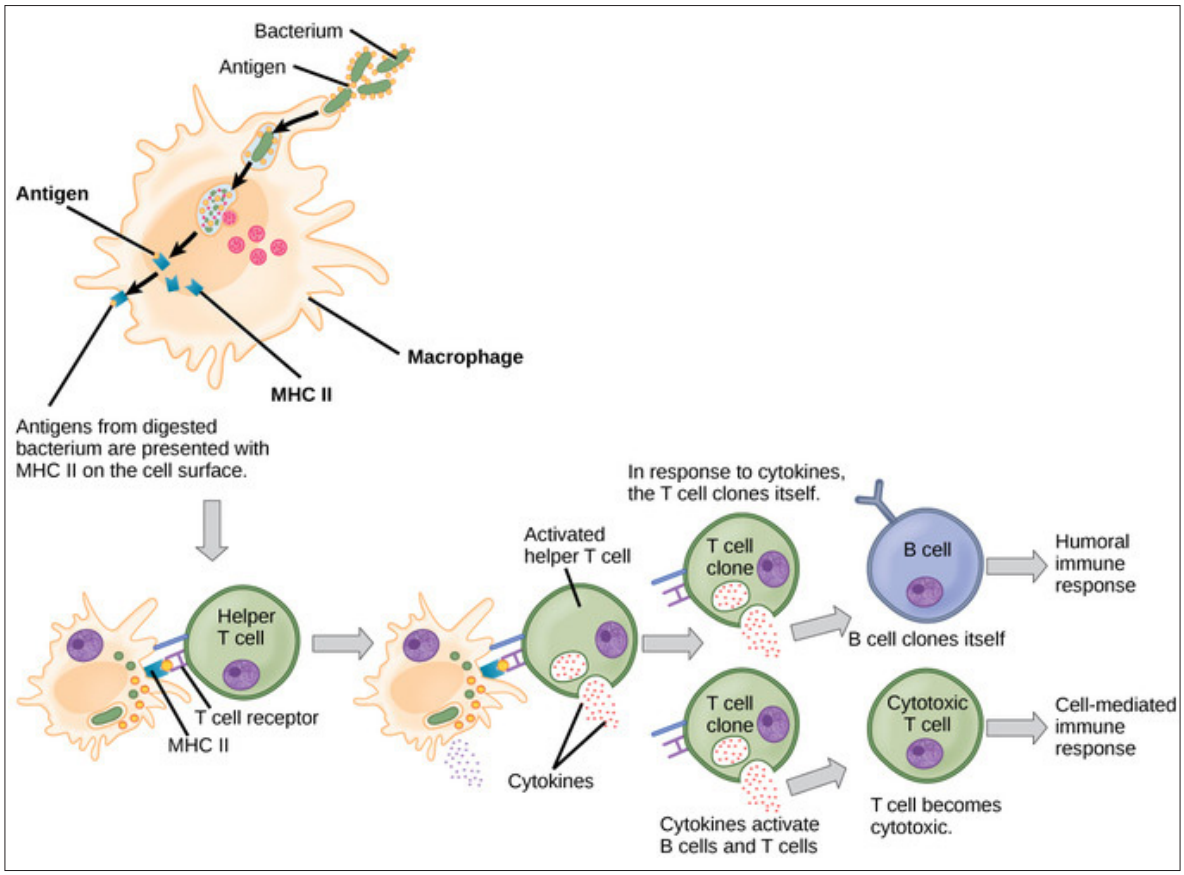
Other factors: Good sleep, stress management, active lifestyle, sufficient intake of water, and meditation can boost immune system.

Supplements: It is always healthy to get nutrients from real foods**,** but supplements can be considered in case of dietary restrictions and food allergies or not getting adequate nutrition from food intake. The national center of complementary and alternative medicine (NCCAM) reported that some dietary supplements may interact with medication or other dietary supplements and may have side effects. Read the labels and information, as some supplements have been found to contain hidden prescription drugs or other compounds and it is important to talk to healthcare provider before taking the supplements.[12]

T cell-mediated immunity

Unlike B cells, T cells can recognize only infected cells by interacting with antigen present on their MHC II molecules. The functionally distinct populations of T cells comprise of helper T cells and cytolytic T cells. Cytokines secreted by the helper T cells facilitate the proliferation and differentiation B cells, macrophages, leukocytes and T cells themselves, as well as other cells. Cytotoxic T cells destroy infected cells by inducing apoptosis and halting the progression of intracellular infections (Fig. 1).

Fig. 1: T cell-mediated immune response



Conclusion

The immune system functions efficiently when adequate levels of micronutrients are present in body. Therefore, it is important intake that the diet contains vitamin A, vitamin B_2, vitamin B_6, vitamin B_{12}, vitamin C, vitamin D, vitamin E, vitamin K, folic acid as well as minerals like iron, zinc, selenium and copper, as all work to improve immune functions in different capacities. Poor diets, processed foods, sugary drinks, lack of fruit and vegetables weaken immune system. Avoiding junk foods, maida, nonveg, deep fried and packaged food is essential, as they affect the immune system poorly.

References

1. *Tong TYN, Key TJ, Gaitskell K, Green TJ, Guo W, Sanders TA, et al. Hematological parameters and prevalence of anemia in white and British Indian vegetarians and nonvegetarians in the UK Biobank. The American Journal of Clinical Nutrition. 2019 Aug 1;110(2):461–72.*
2. *Singh RK, Chang H-W, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med.2017; 15: 73.Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. Nutrients. 2020 Jun;12(6):1562.*
3. *Chand V. Nutrition as a Key Weapon in Strengthening Immune System Relative to Pandemic Novel Coronavirus Disease (COVID-19): A Review. 2020;(8):9.*
4. *Li P, Yin Y-L, Li D, Kim SW, Wu G. Amino acids, and immune function. British Journal of Nutrition. 2007 Aug;98(2):237–52.*
5. *Beaulieu J, Dupont C, Lemieux P. Whey proteins and peptides: beneficial effects on immune health. Therapy. 2006 Jan;3(1):69–78.*
6. *Sivakumar DB, Singotamu DL, Sesikeran DB. NATIONAL NUTRITION MONITORING BUREAU. :166.*
7. *Textbook of Human Nutrition, (Third Edition) by M.S. Bamji, Kamala Krishnaswamy & G.N.V. Brahmam (Eds) - 2009 [Internet]. Biblio.co.nz. [cited 2021 Mar 26]. Available from:* https://biblio.co.nz/book/textbook-human-nutrition-third-edition-ms/d/534091922
8. *Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br J Nutr. 2007 Oct;98:S29-35.*
9. *Maggini S, Pierre A, Calder PC. Immune Function and Micronutrient Requirements Change over the Life Course. Nutrients. 2018 Oct;10(10):1531.*
10. *Mikkelsen K, Apostolopoulos V. Vitamin B12, Folic Acid, and the Immune System. In: Mahmoudi M, Rezaei N, editors. Nutrition and Immunity: Springer International Publishing; 2019:103–14.*
11. *Prasad AS. Discovery of human zinc deficiency: its impact on human health and disease. Adv Nutr. 2013 Mar 1;4(2):176–90.*
12. *Publishing HH. How to boost your immune system [Internet]. Harvard Health. [cited 2021 Mar 26]. Available from:* https://www.health.harvard.edu/staying-healthy/how-to-boost-your-immune-system
13. *T Cells and Cellular Immunity | Boundless Microbiology [Internet]. [cited 2021 Apr 16]. Available from:* https://courses.lumenlearning.com/boundless-microbiology/chapter/t-cells-and-cellular-immunity/

Pro-Con Debate: Should we start broad spectrum antibiotic on day 1 in ICU patients?

Pro: **Dr. Ajith Kumar A K**
Senior Consultant & Head, Dept. of Critical Care Medicine, Manipal Hospital, Bangalore

Con: **Dr. Anupam Prakash**
Professor of Medicine and Head of Dept of Accident and Emergency, Lady Hardinge Medical College & Asso. Dospitals, New Delhi. India.

Early prescription of antibiotics is necessary?

Sepsis is potentially life-threatening and the annual mortality rate due to severe sepsis is comparable to that of acute myocardial infarction.[1] Sepsis is a progressive disease and mortality rate progresses from sepsis to severe sepsis followed by septic shock. Mortality increases exponentially in septic shock patients.[2] A retrospective cohort study by Kumar et al., conducted between July 1989 and June 2004, involving 2,731 adult patients revealed that after the onset of septic shock, every one-hour delay in initiation of antibody leads to increase in the mortality by 7.6%. Hence the delay in initiation of antibiotics is associated with increased mortality rate (Fig. 1).[3] In concurrence with this finding, the study by Ferrer et al. involving 17,990 patients with severe sepsis and septic shock revealed that delay in first antibiotic administration is associated with increased in-hospital mortality (Fig. 2).[4]

Fig. 1: Comparison of cumulative effective antimicrobial initiation with patient fraction

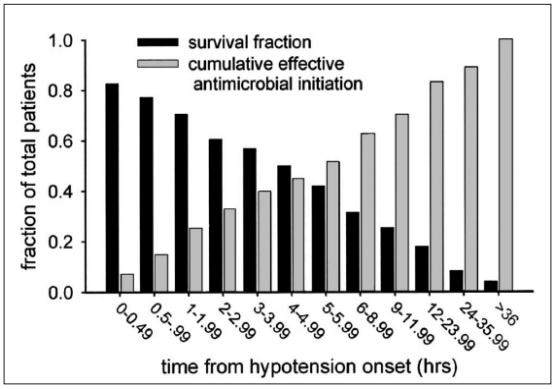
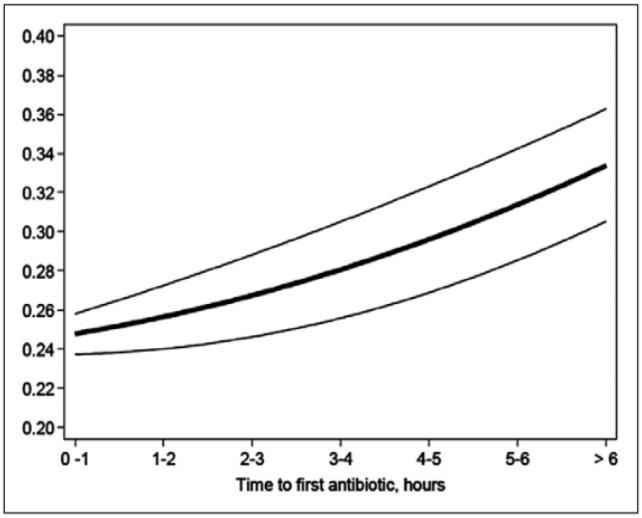


Fig. 2: Comparison of time to first antibiotic initiation to predicted hospital mortality



Surviving sepsis campaign 2016 has highlighted the need to consider sepsis and septic shock as medical emergencies and recommended the immediate initiation of treatment and resuscitation.[5] Surviving sepsis guidelines 2018 condensed the initial resuscitation of sepsis and septic shock to hour-1 bundle.[6] The hour-1 bundle enables clinicians to act swiftly to obtain blood cultures, administer broad-spectrum antibiotics, and initiate fluid resuscitation and vasopressors, if clinically indicated. Based on the study findings involving 3194 patients with community-onset bacteremia, Lee et al. reported that increased risk of delayed defervescence and 30-day mortality are associated with delay in the time-to-appropriate antibiotic, and early administration of appropriate empirical antimicrobials is advocated to manage severe bacteremia episodes.[7]

What is the need for broad-spectrum antibiotics?

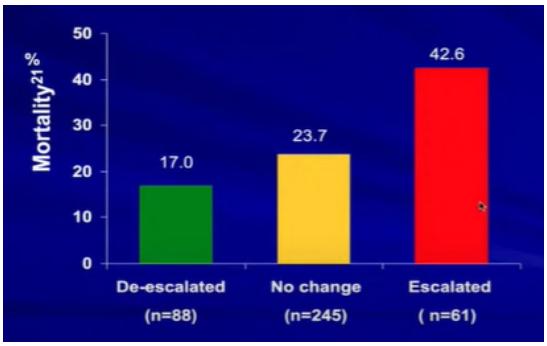
In the Nobel lecture, Alexander Fleming has highlighted the following, " *It is not difficult to make microbes resistant to penicillin and the time may come when penicillin can be bought by anyone in the shops and then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant*". Major resistant Gram-positive pathogens include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, drug-resistant pneumococci, vancomycin-intermediate *Staphylococcus aureus* (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA). Major resistant Gram-negative pathogens include extended spectrum beta-lactamases, multidrug-resistant Acinetobacter, multidrug-resistant Pseudomonas, multidrug-resistant/ pandrug-resistant Klebsiella, and metallo-β-lactamases. A study conducted at 10 participant laboratories by Mathai et al monitored and processed microbiologic specimens of hospitalized patients. The study has noted extended-spectrum β-lactamase (ESBL) phenotypes-mediated resistance in 60% of *E. coli* isolates and in 57% in Klebsiella species.[8] Culture evaluation of the 65 stool samples obtained from patients admitted at a hospital in Chennai has found that nearly 51% of the subjects had colistin-resistant bacterial infection. Kadri et al. reported

that nearly 4165 patients received discordant empirical antibiotic therapy and the treatment was associated with increased odds of overall mortality.[9]

Whether de-escalation is superior than escalation?

In a study involving 398 ICU patients with ventilator-associated pneumonia, Kollef et al. reported that de-escalation of therapy in ventilator-associated pneumonia patients was associated with a reduction in mortality, whereas in case of escalation of therapy, the mortality rate was high (Fig. 3).[10] Guo et al. reported that a metanalysis of 9 studies involving 1847 patients stated that antibiotic de-escalation therapy has no detrimental impact on mortality in patients with severe sepsis and/or septic shock, as compared to the continuation of broad-spectrum antibiotics.[11]

Fig. 3: Mortality rates among patients with ventilator-associated pneumonia



Take home message

- Sepsis and septic shock are medical emergencies.
- Evidence-based guidelines advocate the initiation of empiric broad-spectrum antibiotics with one or more antibiotics within 1 h for patients with sepsis or septic shock.
- Early broad-spectrum antibiotics need to be started in all cases of suspected infections, sepsis, septic shock, and ICU admitted cases.
- De-escalation to narrower spectrum antibiotics needs to be done in 3-4 days.
- Bedside rapid diagnostic tests are the future tools to accurately identify the pathogens involved in multi-drug resistance and reduce antibiotic misuse.

Pro-Con Debate: Should we start broad spectrum antibiotic on day 1 in ICU patients?

Con: Dr. Anupam Prakash

Surviving sepsis guidelines

Although these guidelines are strongly recommended, they have low-to-moderate quality evidence. The 2016 surviving sepsis guidelines are briefed below: [5]

A. Initial resuscitation

- At least 30 mL/Kg of IV crystalloid fluid within first 3 hours
- After initial resuscitation, additional fluids guided by frequent reassessment
- Mean arterial pressure >65 mm Hg
- Guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion

B. Screening of sepsis and performance

C. Diagnosis of sepsis with appropriate cultures

D. Antimicrobial therapy should be initiated immediately after recognition and within 1 hour of sepsis and septic shock. Empiric broad-spectrum therapy should be started with one or more antimicrobials for patients presenting with sepsis or septic shock. It is recommended against sustained systemic antimicrobials prophylaxis in patients with severe inflammatory states of non-infection origin.

Physicians managing critically-ill patients feel greater obligations towards their patients than towards maintenance of the delicate ecological balance of prevalent microbiological threats and resistance patterns. Inappropriate antibiotic therapy is associated with 30%-40% excess mortality in patients with sepsis compared to patients without shock, and the treatment success is determined by appropriate patient selection for each treatment option.[11]

Why initiation of broad-spectrum antibiotics on day 1 in ICU is not necessary?

It is very important to consider the history of patients who get admitted to ICU, profile of disease encountered in ICU, and the type of ICU. A retrospective study conducted by Poluyi et al. among patients admitted to the general ICU of Lagos University Teaching Hospital (LUTH) from 1st of November 2010 to 30th of November 2015 reported that patients referred from the specialty of internal medicine, other than sepsis, were responsible for patient's admission in ICU and mortality (Table 1). None of the patient had sepsis on first day and hence it is not recommended to start broad-spectrum antibiotics on day 1 in ICU.[12] An observational study done in 34 ICUs across India by Singhi et al. between July 2013-September 2014 stated that the corresponding proportion of patients noted with dengue, scrub typhus, meningitis/encephalitis, and malaria were 23%, 18.2%, 9.6%, and 8.1%, whereas the sepsis constituted only 7%.[13] The researchers have noted that only 7% of the ICU sepsis patients required broad spectrum antibiotics on day 1. The 4-day point prevalence study carried out by Divatia et al. between 2010 and 2011 in 4209 patients from 124 ICUs found that 28.3% had severe sepsis or septic shock during ICU stay, whereas 60.7% patients received antibiotics without evidence of infection.[14]

The commonly noted ICU admissions include acute myocardial infarctions, pancreatitis, heat stroke, hyperthermia, hepatic encephalopathy, acute delirium, acute kidney infection, dengue, malaria, enteric fever, pyrexia of unknown origin, unknown or life-threatening diseases.

Table 1: Pattern of admission and deaths according to specialties

Specialty	Total number of admission (%)	Total number of Deaths (%)
Neurosurgery (NSU)	207 (32.0)	136 (34.3)
Obstetrics &Gynaecology	100 (15.5)	52 (13.1)
Internal medicine	119 (18.5)	74 (18.6)
General Surgery	90 (13.9)	52 (13.1)
Cardiothoracic surgery unit (CTSU)	46 (7.1)	23 (5.8)
Burns & Plastic surgery (BPSU)	32 (4.9)	29 (7.3)
Paediatrics	20 (3.1)	12 (3.0)
Orthopaedics	13 (2.0)	6 (1.5)
Paediatrics surgery (PSU)	9 (1.4)	7 (1.8)
Urology	6 (0.9)	4 (1.0)
Ear, Nose & Throat surgery (ENT)	4 (0.6)	2 (0.5)
Oral & maxillofacial surgery (OMFS)	1 (0.1)	0 (0.0)
Total	**647 (100.0)**	**397 (100.0)**

The diagnosis of infection on day 1 is challenging due to the lack of appropriate test. Denny et al. underscored the need to have a rapid point-of-care test that reliably differentiate between individuals who need antibiotics from those who do not. A small number of studies have attempted to compare early aggressive versus conservative antimicrobial strategies in the ICU. However, evidence from these literature studies is not robust enough to guide the clinical practice.[15] Overprescribing and inappropriate use of antibiotics are associated with adverse events and the irrational use of broad spectrum antibiotics, including prescription of incorrect doses, self-medication and treatment of non-bacterial illness, is linked to increasing antibiotic resistance.

Take home message

- It is not advisable to start broad-spectrum antibiotics on day 1 of ICU admission, unless sepsis is confirmed.
- Broad-spectrum antibiotics should be selected with utmost caution in patients suspected with sepsis, as several conditions such as pulmonary thromboendarterectomy, adrenal insufficiency, diabetic ketoacidosis, pancreatitis, anaphylaxis, bowel obstruction, hypovolemia, colitis, vasculitis, toxin ingestion, drug overdose withdrawal syndromes, and medication effects can mimic sepsis.

References

1. *Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Critical Care Medicine. 2001 Jul;29(7):1303–10.*
2. *Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. Crit Care Clin. 2000 Apr;16(2):337–52.*
3. *Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. Critical Care Medicine. 2006 Jun;34(6):1589–96.*
4. *Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014 Aug;42(8):1749–55.*
5. *Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine. 2017 Mar;45(3):486–552.*
6. https://sccm.org/SurvivingSepsisCampaign/Guidelines/Adult-Patients.
7. *Lee C-C, Lee C-H, Yang C-Y, Hsieh C-C, Tang H-J, Ko W-C. Beneficial effects of early empirical administration of appropriate antimicrobials on survival and defervescence in adults with community-onset bacteremia. Critical Care. 2019 Nov 20;23(1):363.*
8. *Mathai D, Rhomberg PR, Biedenbach DJ, Jones RN. Evaluation of the in vitro activity of six broad-spectrum β-lactam antimicrobial agents tested against recent clinical isolates from India: a survey of ten medical center laboratories. Diagnostic Microbiology and Infectious Disease. 2002 Dec 1;44(4):367–77.*
9. *Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. The Lancet Infectious Diseases. 2021 Feb 1;21(2):241–51.*
10. *Kollef MH, Morrow LE, Niederman MS, Leeper KV, Anzueto A, Benz-Scott L, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest. 2006 May;129(5):1210–8.*
11. *Martin-Loeches I, Leone M, Madách K, Martin C, Einav S. Antibiotic therapy in the critically ill - expert opinion of the Intensive Care Medicine Scientific Subcommittee of the European Society of Anaesthesiology. European Journal of Anaesthesiology | EJA. 2017 Apr;34(4):215–20.*
12. *Poluyi EO, Fadiran OO, Poluyi CO, et al. Profile of Intensive Care Unit Admissions and Outcomes in a Tertiary Care Center of a Developing Country in West Africa: A 5 Year Analysis. J Intensive & Crit Care 2016, 2:3*
13. *Singhi S, Rungta N, Nallasamy K, Bhalla A, Peter JV, Chaudhary D, et al. Tropical Fevers in Indian Intensive Care Units: A Prospective Multicenter Study. Indian J Crit Care Med. 2017 Dec;21(12):811–8.*
14. *Divatia JV, Amin PR, Ramakrishnan N, Kapadia FN, Todi S, Sahu S, et al. Intensive Care in India: The Indian Intensive Care Case Mix and Practice Patterns Study. Indian J Crit Care Med. 2016 Apr;20(4):216–25.*
15. *Denny KJ, Wale JD, Laupland KB, Harris PNA, Lipman J. When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit. Clinical Microbiology and Infection. 2020 Jan 1;26(1):35–40.*

FEVER FOUNDATION

Vision

Strive towards imparting knowledge on the unmet needs and provide information on research, education and therapy updates on fever management.

Mission

- Independent, non-commercial foundation supporting the educational / academic activities to address the unmet needs in fever management
- The foundation is committed to conceive, build and sustain programs and make scientific initiatives aimed at providing evidence based updates to the health care professionals
- To run patient education programs on fever management

Objectives of Fever Foundation

- To address the unmet needs and provide updates on fever management
- To provide access to health care through evidence based programs that can reach to large audience
- To engage eminent doctors for various scientific activities

MICRO KNOWLEDGE ACADEMY

PC00042298 MM:5907/10:21